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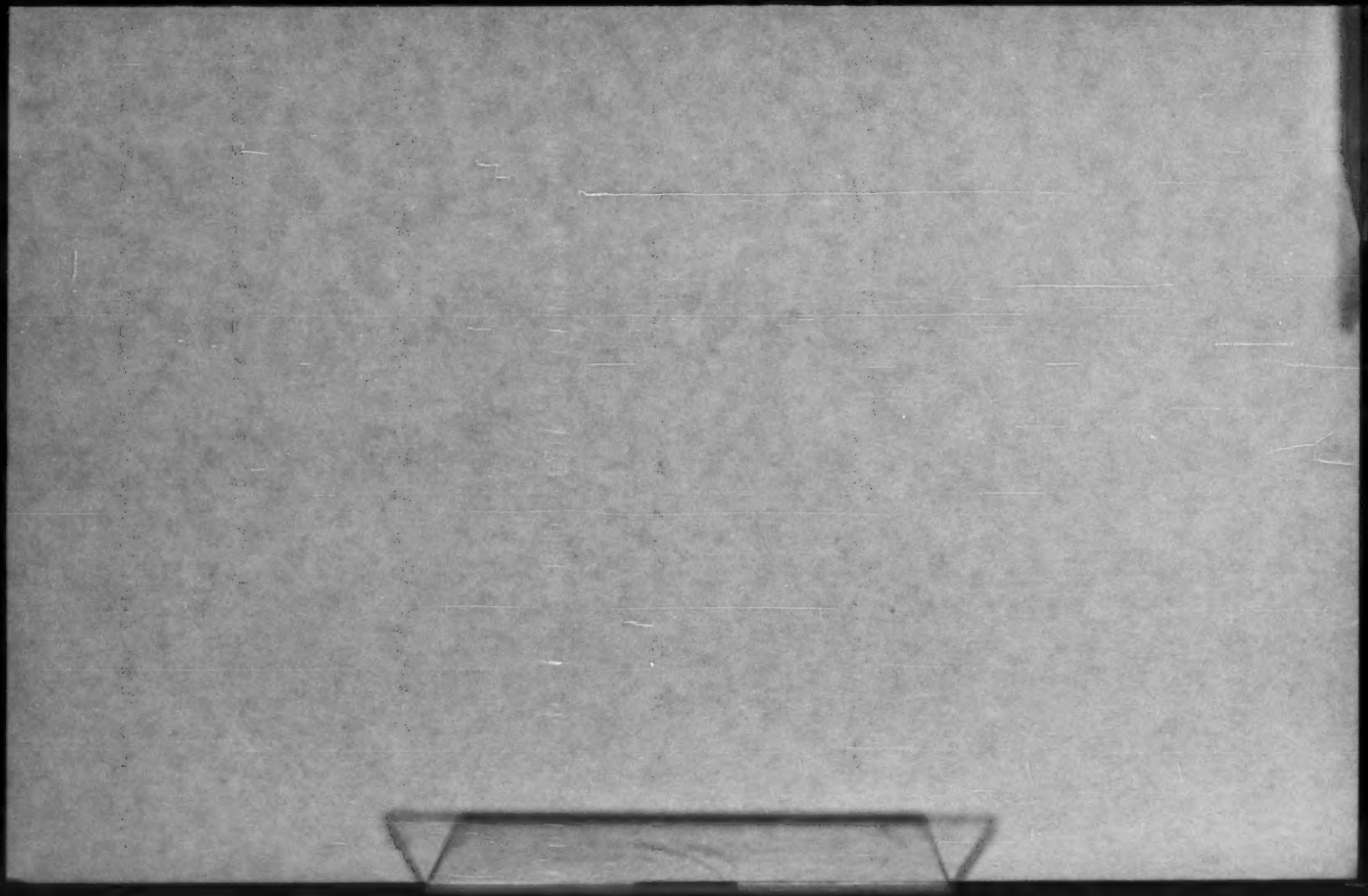

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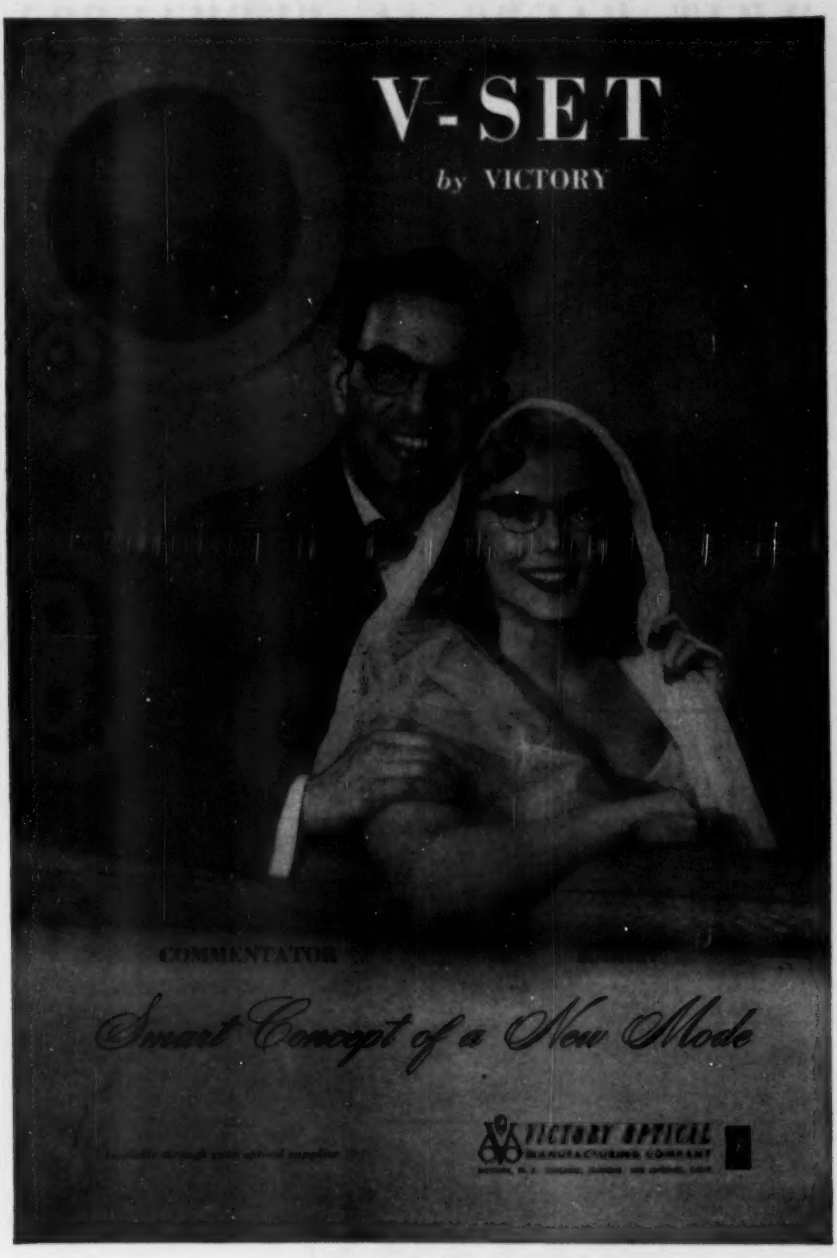
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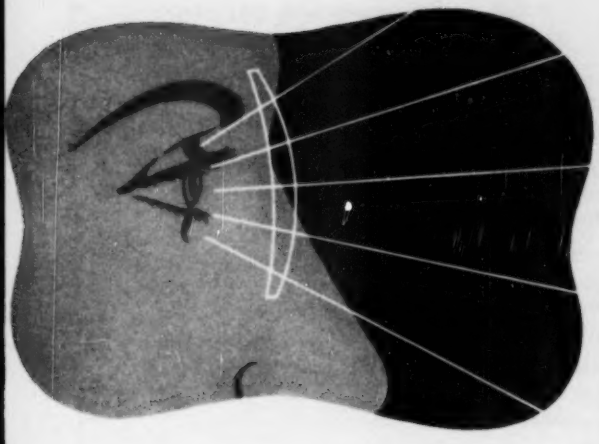

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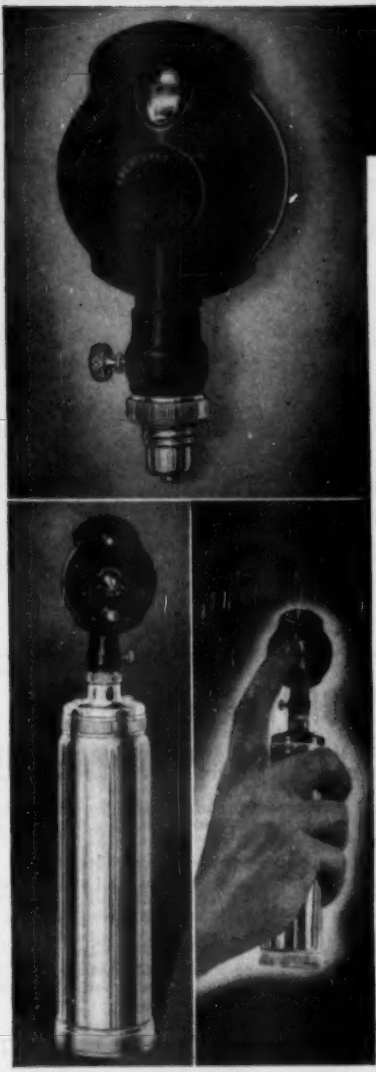

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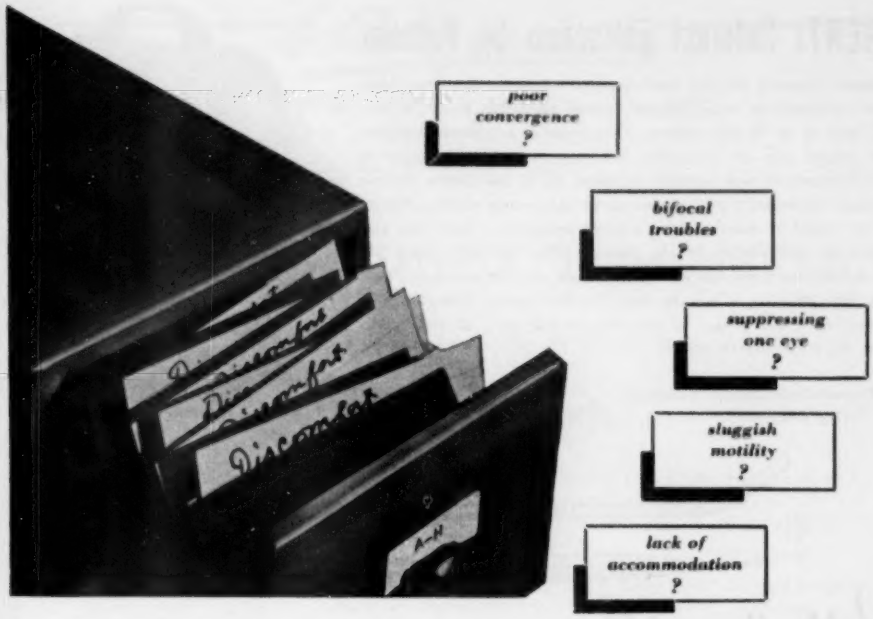

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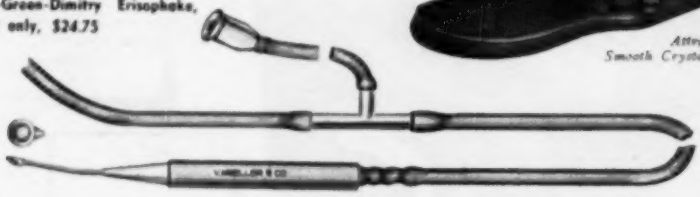

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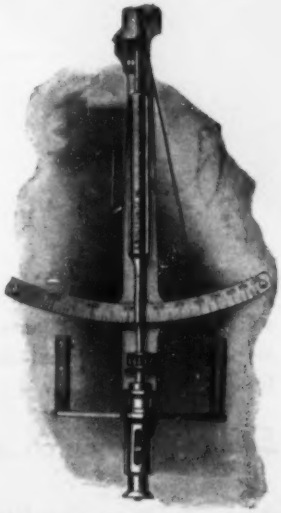

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Editorial

BEGINNING with the July 1950 issue, the ARCHIVES will institute a new department—Annual Reviews—and will eliminate the abstracts from Current Literature. The coverage of abstracts in ophthalmology in the English language is now more than adequate, both in this country and abroad. Section XII of *Excerpta medica* and *Ophthalmic Literature*, both relatively recent publications, extend further the excellent coverage of the field by the *American Journal of Ophthalmology*. It has seemed advisable, therefore, to the Editorial Board of the ARCHIVES to eliminate duplication and to use the space, which is now fast becoming a scarce commodity, for other valuable material.

The colossal growth of all phases of ophthalmology during the last twenty years in both the clinical and the experimental field makes it impossible for the reader to keep abreast of the times without some process of condensation. The menstruum in which the potent principles are offered is of such volume that it cannot be swallowed. Abstracts of the literature, although useful in announcing the material available, give no indication of its value. This can be done only by an expert in the field, who can discriminate between good and bad and who can arrange the material in logical sequence. Thus, the reader will know what is established fact, what is still being debated and what should be discarded because it is based on unworthy evidence.

To achieve this objective, twelve Associates have been chosen from among the large number of outstanding contributors to our knowledge, each of whom is recognized as having special knowledge and interest in a certain phase of ophthalmology. The entire field has been divided into twelve sections, and each month one of these will be covered by one of the Associates. Such a division is obviously artificial and not entirely satisfactory, but it has the advantage of giving the reader each year an intelligent, annotated review of the preceding year's literature.

For example, in July the subject of strabismus will be covered by Dr. Hermann Burian. He will list the articles on strabismus which have appeared in available journals for the year January 1949 to January 1950. The articles which he selects for annotation will be only those which, in his opinion, merit further consideration. He may agree or disagree with the conclusions of the authors, and in his review he will state the reasons for his opinions. Thus, the value of the literature will be considerably enhanced for the reader by the experience of each

month's annotator in the particular field covered. The present Associates will be expected to contribute for three years. The work will be carried on then by others, likewise prominent in each field. In this way, new points of view will be presented continuously and any possible bias avoided. The list of subjects, the month in which each will appear and the annotator are as follows:

Strabismus	July	Hermann Burian
Pharmacology and Toxicology	August	Irving Leopold
The Orbit	September	F. Bruce Fralick
Physiologic Chemistry	October	V. Everett Kinsey
Neuro-ophthalmology	November	C. Wilbur Rucker
Glaucoma	December	Harold G. Scheie
Lids, Lacrimal Apparatus and Conjunctiva	January	James H. Allen
Cornea and Sclera	February	Milton L. Berliner
The Uveal Tract	March	Michael J. Hogan
Lens and Vitreous	April	John G. Bellows
Retina and Optic Nerve	May	A. E. Maumenee
Refraction and Optics	June	Kenneth Ogle

It is hoped that with experience this department will prove to be valuable to all our readers. The Editorial Board will welcome any suggestions and criticism. The section on Ophthalmologic Reviews will continue, and from time to time comprehensive reviews of particular subjects will be published, as formerly.

FRANCIS H. ADLER, M.D.

EFFECT OF DIBENAMINE® IN CHRONIC SIMPLE GLAUCOMA

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AND
HENRY HAIMOVICI, M.D.
NEW YORK

IT HAS recently been shown by one of us [1] that the parasympathomimetic activity consistently demonstrable in the aqueous of nonglaucomatous eyes is either absent or diminished in eyes with chronic simple glaucoma. In the presentation of that work, it was suggested that this parasympathomimetic deficiency might be due either to an actual decrease in the normal acetylcholine content of the aqueous or to an inhibition or counteraction of its effect by other substances. It occurred to us that strong sympathetic stimulation of the eye, by producing an excess of sympathomimetic substance in the aqueous, might cause such a condition. This idea suggested the possibility that chronic simple glaucoma might be associated with ocular adrenergic hyperactivity and, consequently, that therapeutic effects might be produced in that disease through the use of a sufficiently potent sympatholytic drug.

In 1926 Thiel [2] used ergotamine in the treatment of chronic simple glaucoma and reported some therapeutic success. However, the adrenergic activity–blocking effect of this drug is incomplete and is associated with numerous side effects that modify its action. Consequently, its effect on glaucomatous eyes was found to be inconstant, and its use in that disease was abandoned. More recently, however, substances that more specifically block sympathetic nerve impulses have been developed, and of these dibenamine® appears to be the most potent. This drug was therefore employed in our study to secure a clearer evaluation of this approach to the problem of chronic simple glaucoma.

Dibenamine® (N,N-dibenzyl-β-chloroethylamine hydrochloride) has been extensively investigated by Nickerson and Goodman,[3] Hecht and

From the Ophthalmologic Service of the Mount Sinai Hospital.

1. Bloomfield, S.: Relative Deficiency of Parasympathomimetic Activity in Aqueous of Eyes with Chronic Simple Glaucoma, Arch. Ophth. **37**:608 (May) 1947.

2. Thiel, R.: Experimentelle und klinische Untersuchungen über den Einfluss des Ergotamins (Gynergens) auf den Augendruck beim Glaukom, Klin. Monatsbl. f. Augenh. **77**:753 (Dec.) 1926.

3. Nickerson, M., and Goodman, L. S.: Pharmocological and Physiological Aspects of Adrenergic Blockade, with Special Reference to Dibenamine, Federation Proc. **7**:397 (June) 1948.

Anderson,[4] Haimovici [5] and others. These investigations have shown that dibenamine[6a] is a highly specific adrenolytic and sympatholytic drug. Like many other nitrogen mustard derivatives, it is locally irritative and is therefore administered intravenously in high dilution by the slow drip method. Occasional transitory side actions, having their origin principally in the central nervous system, have been reported, such as emotional instability, restlessness or drowsiness, confusion and nausea.

Christensen and Swan [6] have recently studied the effects of dibenamine[6a] on the eye. They reported that in normal eyes miosis and narrowing of the palpebral fissure frequently occur and that a mild decrease in ocular tension is consistently present. They administered dibenamine[6a] to a number of patients with acute congestive and secondary glaucoma and described a consistent and significant fall in intraocular pressure in their eyes. The present investigation has been concerned with the effects of dibenamine[6a] solely on eyes with chronic simple glaucoma and therapeutic possibilities of the drug in that disease.

PRESENT INVESTIGATION

Methods and Material.—The dose of dibenamine[6a] employed in this study was 5 mg. per kilogram of body weight. The desired amount was thoroughly dissolved in 400 cc. of isotonic sodium chloride solution and administered intravenously by the slow drip method. A constant rate of 75 to 100 drops per minute was observed, since side actions are more prone to occur with rapid administration of this drug. After completion of the infusion, the vein was flushed with 100 cc. of isotonic sodium chloride solution U. S. P. in order to prevent local phlebothrombosis. To avoid the possible occurrence of nausea or vomiting, food was withheld for four hours preceding the administration of the drug.

All patients studied were hospitalized during this investigation. For each subject the blood pressure was noted and the ocular tension recorded for several days before the administration of dibenamine.[6a] This was done first during the use of miotic drops and then while all ocular medication was stopped for two days. Complete bed rest was instituted for forty-eight hours after the drug was given. During the infusion, and for at least three days thereafter, simultaneous readings of ocular tension and blood pressure were taken at frequent intervals with the patient flat in bed. A further correlation of ocular and systemic effects of the drug was studied by noting postural changes during this time. This was done by

4. Hecht, H. H., and Anderson, R. B.: The Influence of Dibenamine on Certain Functions of the Sympathetic Nervous System in Man, Am. J. Med. **3**:3 (July) 1947.

5. (*a*) Haimovici, H.: Inhibitory Effect of Dibenamine on Vasconstrictor Substances, Proc. Soc. Exper. Biol. & Med. **64**:486 (April) 1947. (*b*) Haimovici, H., and Medinets, H. E.: Effects of Dibenamine on Blood Pressure in Normotensive and Hypertensive Subjects, ibid. **67**:163 (Feb.) 1948.

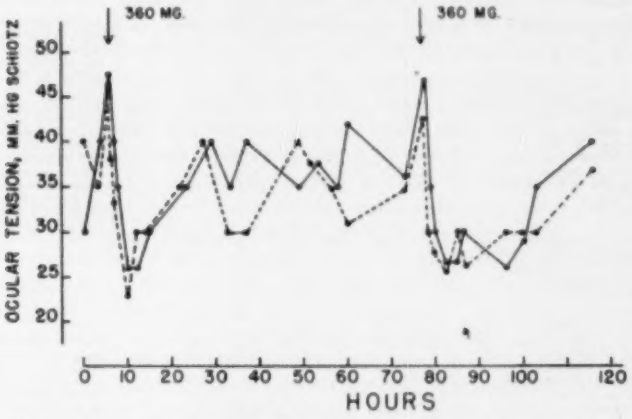
6. Christensen, L., and Swan, K. C.: Adrenergic Blocking Agents in the Treatment of Glaucoma, Tr. Am. Acad. Ophth. (May) 1949, p. 489.

6a. The dibenamine[6a] used in this study was supplied through the courtesy of Dr. W. Gump, of Givaudan-Delawanna Inc., Delawanna, N. J., and the Smith, Kline and French Laboratories, Philadelphia.

recording periodically the blood pressure and pulse rate of each patient while supine, then while sitting and, finally, while standing. In this paper, all measurements of ocular tension are expressed in millimeters of mercury as recorded with the Schiøtz tonometer.

The effect of the drug was studied on 18 eyes in 9 patients, whose ages ranged from 50 to 75 years. Each patient had a history and clinical evidence of bilateral chronic simple glaucoma, without other significant ocular disease. Two of these patients had diabetes mellitus. The effect of the drug on these 2 patients did not differ appreciably from that noted in the other patients, and their diabetic status showed no significant change. Two patients had hypertensive vascular disease. After administration of dibenamine,® both showed a decided drop in the resting blood pressure, followed by a gradual return to the original level within forty-eight hours.

The tension in 9 of these eyes had been satisfactorily controlled, before this study was begun, with drops of 2 per cent pilocarpine hydrochloride administered



Hypotensive effect of dibenamine® in a man aged 58 with chronic simple glaucoma. Tensions in the right eye are indicated by the broken line; tensions in the left eye, by the solid line.

three times daily. However, because use of miotics had been discontinued for at least two days before, 4 of these eyes had tensions above 30 mm. at the time administration of dibenamine® was begun. Although the remaining 5 eyes in this controlled group had tensions below 30 mm. before dibenamine® was given, there was no doubt of the diagnosis, since on several previous occasions each had presented abnormally high tensions.

The tension in the other 9 eyes had not been controlled by the use of one or more cholinergic miotics, which included pilocarpine, physostigmine, carbachol, furfuryl trimethyl ammonium chloride (furmethide®) and diisopropyl fluorophosphate (DFP). Consequently these patients were all in the hospital for surgical treatment of their glaucoma. Two of these eyes had been operated on without success some time before for the disease. No eye in the entire group was aphakic. In all but 1 of the patients, as will be described, eye drops were discontinued for two days before dibenamine® was tried.

Observations.—The accompanying table shows in detail the effect on the tension in all these eyes produced by dibenamine.® The striking fact

Hypotensive Effect of Dibenamine® on Eyes with Chronic Simple Glaucoma

Case	Age, Yr.	Previous Control of Tension and Therapy	Tension Immediately Before Dibenamine (Mm. Hg, Schiøtz) O. D.	O. S.	Lowest Tension Following Dibenamine (Mm. Hg, Schiøtz) O. D.	O. S.	Time Required for Maximum Effect on Tension (Hr.) O. D.	O. S.	Time Required for Return of Tension to Predibenamine Level (Hr.) O. D.	O. S.	Comment
1	69	O. U.: Controlled with pilocarpine	29	29	18	18	5	5	24	24	
2	64	O. D.: Controlled with pilocarpine O. S.: Uncontrolled with pilocarpine, physostigmine or carbachol	46	86	28	45	6	6	48	48	Hypotensive effect of "dibenamine" on left eye similar to that resulting from carbachol administered locally
3	62	O. D.: Uncontrolled with pilocarpine O. S.: Controlled with pilocarpine	38	26	22	16	5	5	30	32	O. D.: Iris atrophied and fixed in mid-dilation by old posterior synechiae; no miotic response to "dibenamine" noted
4	60	O. U.: Uncontrolled with pilocarpine; carbachol; di-isopropyl fluorophosphate, and 4% pilocarpine and 0.5% physostigmine together every 2 hr.	56	50	40	16	6	6	48	48	Administration of 4% pilocarpine and 0.5% physostigmine 6 times daily produced no apparent effect on tension before "dibenamine" and was continued throughout the experiment; 48 hr. after first dose of "dibenamine" a second dose was given, with same hypotensive effect on each eye
5	62	O. D.: Controlled with pilocarpine O. S.: Uncontrolled with pilocarpine and carbachol	47	47	32	20	5	5	48	48	
6	75	O. U.: Controlled with pilocarpine	20	23	20	15	6	6	24	24	
7	80	O. D.: Controlled with pilocarpine O. S.: Uncontrolled with pilocarpine, carbachol and "furmethide"	27	61	22	10	4	6	30	5 wk.	Patient with hypertensive vascular disease; all systemic effects of "dibenamine" subsided in 48 hr., but hypotensive effect on O. S. continued 5 wk., with subsequent control by pilocarpine
8	60	O. U.: Uncontrolled with pilocarpine; pilocarpine and physostigmine, and di-isopropyl fluorophosphate	35	76	23	37	6	6	48	36	Moderate hypertensive vascular disease; 48 hr. after first administration of "dibenamine" effect disappeared, and second dose had less hypotensive effect on eyes; 5 days later "dibenamine" repeated, with effect on ocular tension similar to that of first dose
9	59	O. D.: Uncontrolled with pilocarpine; neostigmine, and pilocarpine and physostigmine O. S.: Controlled with pilocarpine	47	47	23	20	4	4	23	22	72 hr. after first administration of "dibenamine," second dose given, with similar effect on ocular tension, in both degree and duration

revealed is that in each of these 18 eyes with chronic simple glaucoma an appreciable fall in ocular tension occurred, beginning two to three hours after the administration of the drug. In each instance the maxi-

mal reduction in intraocular pressure occurred from four to six hours after dibenamine® was given and thereafter remained at a relatively low level for periods ranging from twenty to forty-eight hours, except in 1 eye, in which the reduction in tension persisted much longer, as will be described. At the end of that time, in all but this eye, the tension gradually rose approximately to the level present before administration of dibenamine.®

Of the 9 eyes whose tension had previously been controlled with 2 per cent pilocarpine hydrochloride, 4 had shown abnormally high tensions before dibenamine® was administered, owing to the discontinuation of use of miotic drops. Under the effect of dibenamine® the tension in all these eyes dropped below 30 mm.—in 1 eye to 28 mm. and in the others to levels between 15 and 23 mm. The relatively low tension produced by dibenamine in these eyes suggests that during its period of activity this drug is at least as effective in controlling tensions as is 2 per cent pilocarpine hydrochloride in eyes that respond to the latter miotic.

The other 9 eyes studied had abnormally high ocular tensions that were not controlled with the usual miotics. In 5 of these eyes, with tensions ranging from 35 to 61 mm., the use of dibenamine,® in the absence of all other medication, reduced the tension to levels ranging from 22 to 30 mm. within six hours and persisting from six to twenty-four hours. One other eye, whose tension had not responded at all to cholinergic drugs, showed a temporary decrease from 76 to 37 mm. after dibenamine.® Another 2 eyes, in a patient in the group with uncontrolled tension, had not responded to pilocarpine, physostigmine, carbachol or diisopropyl fluorophosphate. A further regimen of 4 per cent pilocarpine hydrochloride and 0.5 per cent physostigmine salicylate every two hours had produced no reduction in tension in two days. Dibenamine® was then administered, and the pilocarpine and physostigmine were continued as before. A reduction in tension, from 56 mm. in each eye to 40 and 35 mm., respectively, then occurred within the next few hours, with a gradual return to the original level of 56 mm. in each eye within forty-eight hours, in spite of the continuation of pilocarpine and physostigmine throughout this period. In the remaining eye in this group, dibenamine® administered without other drugs succeeded in reducing the tension, but only to a degree previously attained by carbachol. In summary, of 9 eyes with chronic simple glaucoma previously uncontrolled with cholinergic miotic therapy, 8 showed a greater reduction in intraocular pressure after administration of dibenamine® than after any other medication. In the remaining eye the induced fall in tension equaled that resulting from the miotic previously employed. The action of cholinergic drugs on all these eyes after the effect of dibenamine® had subsided was essentially the same as that observed before the administration of dibenamine.®

The reduction in tension that occurred in the entire series of 18 eyes after a single administration of dibenamine* ranged from 5 to 40 mm. This decrease in tension was measured from the level present just before administration of dibenamine* to the lowest subsequent point, which was reached within six hours in all cases. The reductions that occurred were greater in the eyes whose initial tensions were high and were proportionately less in eyes whose initial tensions were at lower levels. Thus, in the 5 eyes with tensions within normal limits, ranging from 23 to 29 mm., before the drug was given, the average fall was 10 mm. In the remaining 13 eyes, with tensions ranging from 32 to 85 mm., the average fall in tension was 25 mm. It is also of interest to note that the drop in tension was usually approximately the same in the 2 eyes of any one patient if the initial intraocular pressures had been equal.

No correlation could be established between the initial condition of an eye and the duration of the ocular hypotensive effect of dibenamine.* In all but 1 eye the lowered tension resulting from the drug gradually rose to its previous level in twenty to forty-eight hours. In only 1 eye did the effect of dibenamine* last longer than forty-eight hours. This was in a Negro aged 50 with hypertensive vascular disease. In this patient, the intraocular pressure of one eye was satisfactorily controlled with 2 per cent pilocarpine hydrochloride administered three times daily. The tension in the other eye remained abnormally elevated in spite of frequent instillations, at different times, of pilocarpine, carbachol and furfuryl trimethylammonium chloride. After all other medication was stopped, administration of dibenamine* succeeded in reducing the tension in the latter eye from 61 to 30 mm., where it remained without further therapy for five weeks. Thereafter the tension in that eye began to rise but has since been easily held within normal range with 2 per cent pilocarpine hydrochloride instilled three times daily. The other eye showed a mild hypotensive response to dibenamine* that lasted twenty hours. This patient also showed a striking response in blood pressure, which dropped from 166 systolic and 106 diastolic to 110 systolic and 70 diastolic in two hours, and a marked postural hypotension. However, as in other patients, these systemic vascular effects lasted only forty-eight hours; the blood pressure then returned to its previous levels and thereafter showed no unusual change when the patient stood erect.

Three patients were given a second dose of dibenamine* forty-eight, forty-eight and seventy-two hours, respectively, after the first infusion, when the tension in each of the 6 eyes had returned to the previous abnormally high level. In 2 of these patients the hypotensive effect on both eyes produced by the second infusion was approximately the same, both in degree and in duration, as that which followed the first dose of dibenamine.* In the third patient the decrease in tension produced by the second administration of dibenamine* was appreciably smaller than that

which followed the first dose and lasted for a shorter period. To this patient dibenamine® was administered for a third time five days later. The resulting hypotensive effect on his eyes was greater than that which followed the second dose and was approximately equal to that which followed the first administration. These experiments indicate that repeated doses of dibenamine,® when administered at such intervals, produce no cumulative effect on ocular tension.

The ocular effects of dibenamine, aside from its hypotensive action, were few. Miosis was produced in all eyes in which such pupillary change was possible. In 3 eyes no such effect could occur. Two of these 3 eyes were those which received pilocarpine and physostigmine throughout the experiment, and maximal miosis was already present before dibenamine® was given. The third eye presented an extremely atrophic iris and a pupil bound down in middilatation by old posterior synechias. In these 3 eyes dibenamine® caused hypotensive effects, similar to those produced in the other eyes. This observation indicates that the reductions in tension resulting from this drug were not related to its miotic action. In some cases a slight narrowing of the palpebral fissure was noted after administration of dibenamine,® but this effect was slight and inconstant.

In all 9 patients the blood pressure was measured at frequent intervals before, during and after the administration of dibenamine.® These readings were made with the patient in the supine position. In the 2 patients with hypertensive vascular disease, a decided drop in resting blood pressure occurred within one hour after administration, followed by a gradual return to the original level in forty-eight hours. In the 7 patients with normal blood pressure, the effect of dibenamine® on the resting vascular tension varied. In 3 of these subjects with normal blood pressure a moderate decrease in blood pressure followed administration of the drug; in 3 others a mild fall of questionable significance occurred, and in the remaining patient no appreciable change was observed. These observations are in accord with the effects on blood pressure previously reported.[25b]

After administration of dibenamine,® postural hypotension occurred both in patients with hypertensive vascular disease and in those with normal blood pressure. Of 8 patients studied for orthostatic effects, only 1 failed to show a significant fall in blood pressure and an increase in pulse rate when in the erect position. Because of the frequent severity of the postural effects on blood pressure induced by dibenamine,® it is necessary that patients be kept flat in bed for thirty-six to forty-eight hours after its administration.

The possibility of a correlation between the hypotensive effect on the eyes of dibenamine® and its effect on blood pressure and postural tension was investigated. Because of the small number of patients involved,

definite conclusions could not be drawn. However, it is apparent from these data that no quantitative relation exists. The effect on ocular tension as a rule did not parallel in degree the changes in resting blood pressure that occurred, and severe postural hypotension was noted in patients with moderate, as well as marked, changes in intraocular pressure.

Other constant, but transient, systemic effects of dibenamine® were dryness of the mouth, stuffiness of the nose and increased warmth and dryness of the extremities, especially of the palms and soles. These are all attributable to the sympatholytic effects of the drug.

Toxic side effects due to dibenamine® were generally mild and uniformly transient. These consisted of nausea and vertigo (1 case), drowsiness (4 cases), crying (1 case) and mild confusion (2 cases). All these symptoms occurred in the latter part of the administration of the drug and disappeared completely within forty-five minutes after the infusion was completed. At the end of that period no further manifestations of this sort occurred in any patient. Two patients complained of moderate pain along the vein during the course of the infusion, and 1 of these patients subsequently had mild phlebothrombosis, which responded readily to local therapy. Careful administration of dibenamine® and subsequent complete bed rest for thirty-six to forty-eight hours appeared to be important factors in preventing or reducing to a minimum the side effects of this drug.

COMMENT

Although the number of patients treated with dibenamine® in this study is not large, the effects on ocular tension observed were so constant that certain conclusions may justifiably be drawn. It is apparent that the intraocular pressure of eyes with chronic simple glaucoma is reduced significantly by the intravenous administration of dibenamine.® This hypotensive effect apparently occurs not only in eyes whose tensions have previously responded satisfactorily to the usual miotics but also in many eyes in which parasympathomimetic drugs have proved ineffectual. A single dose of dibenamine® usually begins to exert its effect on intraocular pressure within three hours, produces its maximum reduction within six hours and generally loses its effectiveness within forty-eight hours. Repeated administration after that period produces no additive effect.

Despite this demonstration of the very effective hypotensive action of dibenamine® on eyes with chronic simple glaucoma, its clinical value as a therapeutic agent in this disease appears to be limited. The necessity for its intravenous administration by the slow drip method, and its marked systemic effects, lasting about forty-eight hours, render its routine use in treatment of this condition impractical. The only justifiable thera-

peutic indication for its administration in a case of chronic simple glaucoma would appear to be a high preoperative tension which does not respond to other treatment. However, even in these circumstances, it is questionable whether dibenamine® should be employed in preference to such surgical measures as posterior sclerotomy or other slowly decompressive procedures.

Nevertheless, it must be borne in mind that dibenamine® is one of the first of a newly developed group of effective sympatholytic agents. As such, its study should be considered primarily as an exploration of the general potentialities of that group. The evidence here presented indicates that such drugs do produce hypotensive effects in eyes with chronic simple glaucoma and that in some cases this effect is greater than that resulting from the use of parasympathomimetic drugs. Such a demonstation suggests a new, potentially valuable approach in the treatment of that disease, through the use of these recently developed adrenergic activity-blocking agents. Continued study of related pharmacologic substances may reveal some that can be administered more conveniently than dibenamine,® with minimal systemic effects, and possibly with a longer period of ocular hypotensive activity.

The precise mechanism whereby dibenamine® affects intraocular pressure is not apparent. The hypotensive effect produced by the drug in this study was not dependent on the miosis that commonly occurred in these patients as an associated manifestation of sympathetic inhibition. This is evident from the fact that the intensity of miosis generally was not related to the degree of change in ocular tension. Furthermore, in 3 eyes no change in the pupil was observed, although marked decreases in ocular tension occurred. Similarly, the ocular hypotensive action of dibenamine® was apparently not due to the fall in systemic blood pressure, since the former was a constant feature of the action of the drug, whereas the latter was variable in occurrence and usually no proportionate relation between the two could be found. Whatever the exact mechanism may be whereby dibenamine® causes a fall in intraocular pressure, this effect is most probably due to the potent sympatholytic action of the drug, since it occurs as constantly after the administration of the drug as do other manifestations of adrenergic inhibition, such as postural hypotension, stuffiness of the nose and vasodilatation of the extremities. It is noteworthy that Christensen and Swan [6] showed that dibenamine® consistently reduced the tension in eyes with acute congestive and with secondary glaucoma. Since our study has demonstrated that the drug has a similar effect in eyes with chronic simple glaucoma, it would appear that this sympatholytic agent produces its hypotensive action by a mechanism that may be effective in all conditions associated with elevated ocular tension, and thus offers a range of application greater than that provided by cholinergic drugs.

The hypotensive effect of dibenamine® in eyes with chronic simple glaucoma is also of interest as another indication of the important role played by the autonomic nervous system in the control of intraocular pressure, and perhaps in the pathogenesis of that disease. It has been suggested by Elwyn [7] and others that chronic simple glaucoma may be due to a deficiency in parasympathetic stimulation of the eye. The therapeutic effectiveness of the local instillation of parasympathomimetic drugs and the diminished parasympathomimetic activity of the aqueous in this condition [1] have lent support to this theory. The present demonstration that sympatholytic drugs, as represented by dibenamine,® may also produce hypotensive effects in eyes with chronic simple glaucoma indicates that adrenergic hyperactivity may be a factor in the pathogenesis of that disease. The latter possibility is not necessarily a contradiction of the former theory, since the cholinergic and adrenergic systems frequently play opposing roles in physiologic processes, and it is possible that inhibition of the sympathetic nervous system by a drug such as dibenamine may indirectly increase the relative effect of parasympathetic stimuli to the eye.

SUMMARY

Dibenamine® administered intravenously reduced the tension in each of 18 eyes with chronic simple glaucoma, many of which had not responded satisfactorily to cholinergic drugs.

This hypotensive effect was generally maximal within six hours after administration of the drug and then gradually disappeared in all but 1 eye within twenty to forty-eight hours.

The necessity for the administration of dibenamine® by slow intravenous drip and its pronounced systemic effects greatly limit the usefulness of the drug in the routine treatment of chronic simple glaucoma.

The hypotensive action of dibenamine® in eyes with chronic simple glaucoma indicates the potential therapeutic value of a newly developed group of effective sympatholytic drugs and may throw further light on the role of the autonomic nervous system in the pathogenesis of that disease.

1010 Fifth Avenue.

1148 Fifth Avenue.

7. Elwyn, H.: Nature of Glaucoma, Arch. Ophth. **38**:506 (Oct.) 1947.

STUDIES ON THE CRYSTALLINE LENS

I. Technic for in Vitro Culture of Crystalline Lenses and Observations on Metabolism of the Lens

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AND
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THE NEED for an in vitro method of cultivating lenses which would be suitable for performing quantitative metabolic studies over periods of twelve to twenty-four hours gave rise to the present investigation. The apparently limitless possibilities for experimentation on the lens, were it possible to maintain lenses in a normal physiologic state for a relatively indefinite period, stimulated us to perform several preliminary experiments, using different culture mediums, in an attempt to establish such conditions. In this paper a technic is described for culturing lenses, as well as observations on changes in carbohydrate metabolism—a sensitive index of damage—which lenses undergo when incubated in different mediums for periods of approximately a week.

Previous methods of culturing lenses have been based on a perfusion technic devised by de Haan.[1] Bakker,[2] for example, placed rabbit lenses in a shallow air-tight and water-tight glass chamber and then perfused the lenses with sterile Ringer's solution which had remained in the peritoneal cavity of a rabbit for several hours. Under these conditions lenses retained their transparency and their power to heal small abrasions over a period of three weeks.[3] Bakker [4] found also that, for several days

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From the Department of Chemistry, Boston University, and the Howe Laboratory of Ophthalmology, Harvard Medical School.

This paper is part of a dissertation submitted by Mr. F. C. Merriam in partial fulfilment of the requirement for the degree of Doctor of Philosophy from Boston University.

1. de Haan, J.: Le mode de croissance des cellules migratrices dans les cultures in vitro à irrigation permanent, Bull. d'histol. appliq. à la physiol. **1**:293-317, 1927.

2. Bakker, A.: Eine Methode, die Linsen erwachsener Kaninchen ausserhalb des Körpers am Leben zu erhalten, Arch. f. Ophth. **135**:581-592, 1936.

3. Bakker, A.: Die Regeneration der verwundeten Linsenkapsel von Kaninchenlinsen in der Durchströmungskultur, Arch. f. Ophth. **136**:333-340, 1936.

4. Bakker, A.: Ueber die Bedeutung der Askorbinsäure (Vitamin C) für den Stoffwechsel der Linse, Arch. f. Ophth. **136**:166-171, 1936.

at least, the lens contained the normal concentration of ascorbic acid and that the oxygen uptake remained essentially constant at 4 microliters per hour per lens.

Weekers [5] analyzed fluid which had been equilibrated with blood and found that it had a higher protein and a lower glucose content than had aqueous humor. He stated that substances (not named) which are secreted into the aqueous humor are not present in the fluid obtained from the peritoneal cavity.

Von Bahr,[6] who studied the effect of calcium deficiency on the metabolism of surviving lenses, also used the perfusion method. For this purpose fluid resulting from intraperitoneal injection into rabbits, as used by Bakker, was unsuitable, since it contained too much calcium. Von Bahr perfused lenses with 1 to 2 drops per minute of a synthetic medium containing a small amount (0.7 per cent) of blood serum. He reported that lenses remained clear and transparent for several days, and "if good conditions were maintained" for at least ten days. Occasionally peripheral opacity was noted, which he thought resulted from trauma—incident on preparation of the lens—acting on the zone of young growing cells at the equator. No analyses were performed on the lens to indicate the constancy of metabolism of the lens during the period of incubation.

The perfusion procedure has the advantage that the lens is bathed continuously by a relatively large volume of solution of unvarying composition. For investigation of the metabolism of the lens the perfusion procedure has the disadvantage, however, that changes in the composition of the fluid are small. Bakker [2] recognized this difficulty in attempting to determine the dextrose consumption of a lens cultured by the perfusion method, since he could not determine any change in concentration of this substance during the period the bathing solution was in contact with the lens. He found it necessary to remove the lens from the perfusion chamber, place it in a separate vessel containing the perfusion fluid and then measure the dextrose concentration at the end of an eight hour period. Under these conditions, 1.8 mg. of dextrose was consumed per day.

To overcome the disadvantage of the perfusion method in making quantitative measurements of lens metabolites, we devised a "batch" technic. In this procedure, significant changes occur in the concentration of various substances in the fluid bathing the lens. Certain disadvantages which are not encountered in the perfusion method are inherent in the

5. Weekers, R.: Cristallin en survie selon la technique de de Haan-Bakker: Composition du milieu nutritif, Compt. rend. Soc. de biol. **131**:140-142, 1939.

6. von Bahr, G.: Influence of Calcium Deficiency on the Surviving Rabbit's Lens: An Experimental Study on the Pathogenesis of Cataracta Tetanica, Acta Ophth. **18**:170-189, 1940.

batch technic; for example, (*a*) utilization of metabolites by the lens during the incubation period may result in partial depletion, (*b*) production of lactic and other acids tends to reduce the p_H of the solution and (*c*) accumulation of other waste products may adversely influence the metabolism of the lens.

These difficulties may be overcome in part, without sacrificing the advantages of the batch technic, by employing a bathing solution which initially contains slightly higher concentrations of metabolites and buffers than those found in aqueous humor. No means of eliminating waste

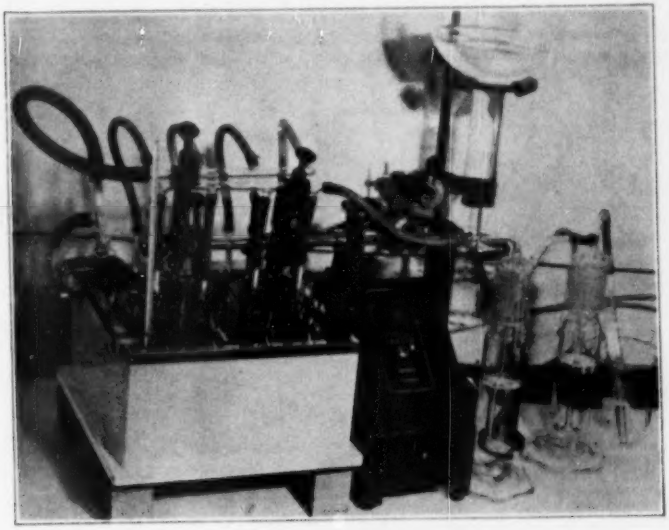

Fig. 1.—Apparatus for lens culture.

products is apparent other than to change the solution at frequent intervals.

PRESENT STUDY

Apparatus.—The apparatus (fig. 1) was designed to provide the lens with an environment similar to that in which it exists in vivo. It consists of (1) a culture tube containing a nutrient medium; (2) a gas-distributing system to supply oxygen for respiration, and carbon dioxide for maintenance of the carbon dioxide-bicarbonate buffer system; (3) a mechanical rocker to minimize local differences in concentration of metabolites or waste products due to slow diffusion within the fluid, and (4) a water bath to maintain constant temperature. In addition, traps were provided for absorbing waste carbon dioxide when radioactive substrates were employed.

The culture tube (fig. 2) has a wide opening (*A*) for ready withdrawal and replacement of fluid under sterile conditions, smaller openings (*C* and *B*) for entrance and exit of the gas mixture and a pit (*D*) to hold the lens. All openings are plugged with cotton, and the tube is sterilized with heat before use.

Four culture tubes are suspended side by side from the arm of a Burrell (model A) mechanical shaker and immersed in a water bath of constant temperature, maintained at 37 to 37.5 C. Water is maintained at constant level by means of a siphon connected to a beaker, which is kept full of water from an inverted flask, which fixes the water level. A synchronous motor with built-in gears was substituted for the original motor in the shaker. This motor rotates the shaft holding the tubes through an angle of 25 degrees at the rate of 2 cycles per minute. The culture tubes are mounted on the shaft with single buret clamps.

A gas mixture of any desired composition is provided from a tank and proportioned among the four tubes by inserting 7 cm. lengths of 0.05 mm. (inner diameter) marine barometer tubing into the rubber tubes which connect the small end

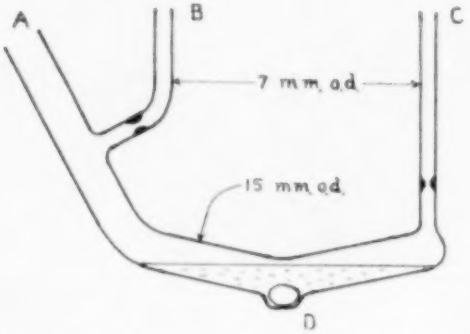

Fig. 2.—Lens culture tube. The outer diameters (*o.d.*) of the tubes are indicated.

of each culture tube to a distributing manifold. In experiments using radioactive material, to be reported elsewhere, the side arm of each culture tube is connected to an exhaust manifold (fig. 1). Both intake and exhaust manifolds are clamped to the rocker shaft.

The gas mixture is partially saturated with water vapor by passing it through a bubbler containing distilled water; the bubbler is immersed in one corner of the water bath. This gas mixture is fed into the manifold at a pressure of about 10 pounds per square inch. While the gas reaching the culture tubes is not completely saturated at 37 C., because of the effect of reducing the pressure at the orifices, the rate of flow required to maintain an essentially constant mixture above the lens is so low that no appreciable amount of water evaporates from the culture medium.

Incidentally, without the lenses being removed from the culture tubes, they may be observed with a biomicroscope, using slit lamp illumination. This can be done by removing the culture tube from the water bath and mounting it with one edge of the pit of the tube touching a mirror placed at 45 degrees from the horizontal.

Bathing Fluid.—Two base synthetic culture fluids were prepared which were approximately isotonic with aqueous humor. The first solution (table, column 1) was based on a Krebs-Henseleit mixture [7] slightly altered in an attempt to duplicate the composition of aqueous humor on the basis of knowledge available at the time the solution was prepared. The p_H of solution 1 at 37 C. in the gas mixture employed was 7.4. After a rabbit lens was incubated for twenty-four hours in 4 ml. of this solution, the p_H fell to approximately 7.0.

The second solution (table, column 2) was based on more recent analyses of the aqueous humor of the rabbit eye.[8] This differs from the preceding medium in the bicarbonate content and the presence of lactic acid and urea. After incubation of a lens for twenty-four hours with 5 ml. of this solution, the maximum change in p_H was from 7.5 to 7.3.

A third medium consisted of beef aqueous humor which was obtained within fifteen minutes after the death of the cattle; it was frozen at once and maintained

Synthetic Culture Mediums

	Solution 1 (Ml.)	Solution 2 (Ml.)
Sodium chloride (0.89%)	116.0	100.0
Potassium chloride (1.19%)	4.7	5.0
Calcium chloride (1.22%)	2.5	1.0
Magnesium sulfate heptahydrate (3.82%)	1.2	0.6
Monobasic potassium phosphate (2.11%)	1.2	1.0
Sodium bicarbonate (1.30%)	24.5	42.0
Dextrose *	2.2 (10.0%)	1.0 (10.0%)
Lactic acid * (80%)	...	0.06
Urea * (8.2%)	...	0.5
Total	152.2	151.16

* All solutions were isotonic with aqueous humor unless starred. Those not isotonic were added in such small amounts that the final solution was not appreciably different from 152 milliosmoles.

in this state until sterilized by Berkefeld filtration. The glucose concentration of the aqueous humor was increased from 63 to 218 mg. per hundred cubic centimeters by adding a 1.0 per cent solution of dextrose.

The solution of bicarbonate used in solutions 1 and 2 was saturated with carbon dioxide and was added separately to the culture medium just prior to sterilization.

We have used a volume of 4 or 5 ml. of bathing solution and have changed the solution at twenty-four hour intervals. Incidentally, the natural rate of flow of aqueous humor in the rabbit is approximately 4 ml. in twenty-four hours.[9]

7. Dixon, M.: Manometric Methods as Applied to the Measurement of Cell Respiration and Other Processes, ed. 2, New York, The Macmillan Company, 1943, p. 82.

8. Kinsey, V. E.: Unpublished data.

9. Kinsey, V. E., and Bárány, E.: The Rate of Flow of Aqueous Humor: II. Derivation of Rate of Flow and Its Physiologic Significance, Am. J. Ophth. **32**:189-201, 1949.

Gas Mixture.—Five per cent carbon dioxide and air was used as a gas mixture for all the experiments. The total gas flow for the four culture tubes was adjusted to approximately 1 liter per hour at standard temperature and pressure.

Preparation of Lenses.—Rabbit lenses were used exclusively in this study and were excised by a procedure described by Bakker.[9] The procedure consists in sterilizing a freshly removed eye with approximately 1 per cent iodine in 70 per cent ethyl alcohol and then mounting it, cornea down, on the end of a glass tube which is shaped like a golf tee. Incisions in the shape of a cross are made through the sclera from the optic nerve to within 1 mm. of the cornea. The sclera is then folded down over the edge of the tube to expose the lens. After the lens is freed from its zonular fibers, it is transferred with a sterile loop to a culture tube in such a way that when the lens is allowed to slide slowly into the pit of the tube it rests on the posterior pole.[10] The culture medium is added after the lens is in place.

Analytic Procedures.—Lactic acid was determined by the micromethod of Barker and Summerson,[11] and glucose, by the ferricyanide method of Folin.[12]

Glutathione was extracted from lenses with 1 per cent aqueous trinitrophenol and analyzed by iodate titration in the usual manner. In experiments in which lenses were kept in vitro for a week or more, little ascorbic acid was present in the lens extracts, but in experiments of short duration and in fresh lenses the iodate titration value for glutathione was corrected for the quantity of ascorbic acid present. The latter was determined by titration with sodium 2,6-dichlorophenolindophenol in water.[13]

Results.—Several experiments were performed to determine whether the lens in vitro would retain its transparency and normal metabolic activity. In the first experiment, two lenses were incubated in culture medium. 1. Daily measurements were made on the dextrose consumed and the lactic acid produced, and the lenses were examined to determine whether transparency was maintained. After fifteen days the experiment was terminated. The dextrose consumption and lactic acid production appeared to decrease during the first few days and then remain constant. Because of technical difficulties, the values for dextrose consumption and lactic acid production for the first several days were questionable. However, the lenses remained essentially clear, except that near the end of the incubation period the periphery appeared slightly gray. This effect was also noted by von Bahr,[9] who stated the belief that it might arise from damage incurred during excision to the very young cells situated in the periphery. The glutathione concentration at the end of fifteen days in the cultured lenses was 114 and 128 mg. per hundred grams of wet

10. In instances in which the capsular epithelium was cut off from the solution by resting on the bottom of the tube, certain metabolic reactions were retarded.

11. Barker, S. B., and Summerson, W. H.: Colorimetric Determination of Lactic Acid in Biological Material, J. Biol. Chem. **138**:535-554, 1941.

12. Folin, O., and Malmros, H.: Improved Form of Folin's Micro Method for Blood Sugar Determinations, J. Biol. Chem. **83**:115-120, 1929.

13. Mindlin, R. L., and Butler, A. M.: Determination of Ascorbic Acid in Plasma: Macromethod and Micromethod, J. Biol. Chem. **122**:673, 1938.

tissue, as compared with a normal concentration of from 370 to 400 mg. per hundred grams of wet tissue found for fresh lenses in the same weight group.

In an attempt to minimize the previously observed change in carbohydrate metabolism and loss of glutathione, a second experiment was performed in which amino acids in the form of amigen®[14] (a casein hydrolysate) fortified with aminoacetic acid were added to the medium in an amount which gave a final amino acid concentration of 66 mg. per hundred cubic centimeters.

As a control, the other lens of the same rabbit was cultured in unsupplemented medium. The results are shown in figure 3. The dextrose consumption and lactic acid production in both these lenses fell slightly, and to about the same extent, during the course of incubation. The amount of lactic acid recovered from the lens cultured in the

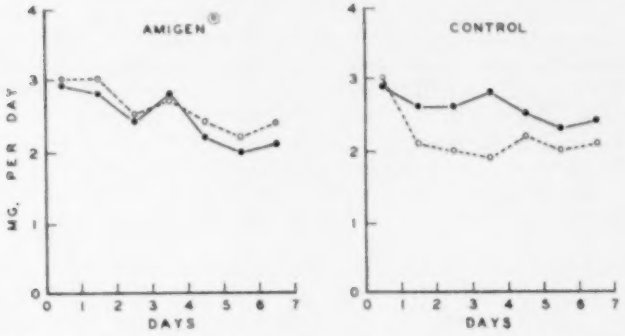

Fig. 3.—Effect of amino acids on metabolism of the lens in vitro. The values for dextrose consumption are indicated by a solid line with dots; values for lactic acid production, by the line of dashes and circles.

medium containing the amino acids exceeded slightly the dextrose consumed, whereas from the control lens culture the amount of lactic acid recovered was less than the dextrose consumed. The difference in dextrose consumed and lactic acid produced presumably represents the loss of the latter due to respiration. The final concentration of glutathione in the lens maintained on the amigen®-supplemented medium was 320 mg. per hundred grams of wet tissue, as compared with 185 mg. per hundred grams of wet tissue in the control lens. The lens cultured for six days in the amino acid–supplemented medium remained clear but for the appearance toward the end of the period of a slight haze in the anterior cortex. Some turbidity at the periphery developed in the control lens.

14. Amigen® was supplied by Mead Johnson Company, Evansville, Ind.

The second synthetic medium (table, column 2) was used for the third experiment. The average results with 2 lenses cultured in this medium are shown in figure 4 *A*. The final concentrations of glutathione were 202 and 252 mg. per hundred grams of wet tissue. The lens having the higher terminal concentration of glutathione remained clear throughout the period of culture; in the other lens a slight diffuse surface opacity developed.

A fourth experiment was carried out in which 2 lenses were incubated in beef aqueous humor fortified with sufficient dextrose to give a final concentration in the medium of 218 mg. of dextrose per hundred cubic centimeters. The average dextrose consumed and lactic acid recovered are shown in figure 4 *B*. The concentrations of glutathione in the 2 lenses at the end of the experiment were 272 and 255 mg., respectively, per hundred grams of wet tissue. The lenses remained clear

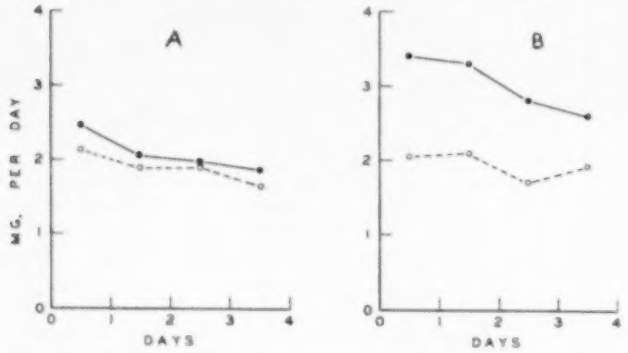

Fig. 4.—*A*, metabolism of the lens in an improved synthetic medium (average for 2 lenses). *B*, metabolism of the lens in beef aqueous humor (average for 2 lenses). The values for dextrose consumption are indicated by a solid line with dots; values for lactic acid production, by the line of dashes and circles.

throughout the period of incubation. In all instances the final culture solution was found to be sterile.

COMMENT

The majority of the lenses cultured by the batch technic remained transparent for periods as long as fifteen days except for slight superficial opacity at the periphery.[15] The utilization of dextrose and

15. Similar opacities were not observed in more recent experiments in which a gas mixture was employed composed of 5 per cent oxygen, 5 per cent carbon dioxide and 90 per cent nitrogen, instead of 5 per cent carbon dioxide in air. This change in gas mixture gives an oxygen tension value more closely resembling that existing in aqueous humor (Pierce, H. F.; Friedenwald, J. S., and Freeman, D.: The Gas Content of the Intra-Ocular Fluid, Am. J. Physiol. **104**:553-556, 1933).

production of lactic acid, however, decreased during the course of incubation. The concentrations of glutathione and ascorbic acid at the end of the experiments were also less in these lenses than in lenses freshly removed from the eye. These changes in metabolism appear to represent more sensitive indexes of injury to the lens than does the physical appearance and suggest that loss of transparency may be a relatively late secondary effect of metabolic changes.

In instances in which lenses were observed to show cortical opacities the glutathione content was reduced to approximately one third or less of normal. These results correlate well with those obtained previously on cataractous lenses taken directly from animals.

The cause of the progressive decrease in rate of carbohydrate metabolism is not apparent. In the case of the experiments carried out with synthetic mediums, it might be thought that a gradual depletion occurs in vitamins which are known to act as prosthetic groups for enzyme systems. To the extent that beef aqueous humor still retains a complement of vitamins to which the lens is normally exposed, this explanation would not apply to the experiments using this culture medium. Experiments using synthetic mediums containing various vitamin supplements are now in progress. These and other changes in the components of the mediums may provide the added information necessary to account for the changing metabolic rates. No conspicuous differences were observed in the relative decrease in dextrose consumption or lactic acid production in any of the three mediums. The glutathione content of the lenses was maintained at more nearly normal levels in the artificial medium supplemented with amino acids. This suggests that glutathione may be synthesized by the lens. In the medium supplemented with amino acids the amount of lactic acid produced was greater than could be accounted for on the basis of the dextrose consumed, presumably because part of the lactic acid was derived from the amino acids. However, the lactic acid recovered from cultures carried out in beef aqueous humor not only did not exceed, but was considerably less than, the dextrose consumed. Whether oxidative destruction of lactic acid in the latter instance, which, incidentally, was much greater than that occurring in cultures maintained on unsupplemented mediums, was sufficient to mask production of lactic acid from amino acids in the aqueous humor cannot be stated in the absence of independent measurements of lactic acid consumed (respiration).

The in vitro conditions are not yet developed to the point where lenses may be cultured indefinitely without loss of physiologic integrity; however, for a period of the first twenty-four hours the method outlined, unlike the perfusion technic, appears to be entirely adequate for conducting quantitative metabolic investigations.

SUMMARY

A batch technic for cultivating lenses in vitro which is suitable for performing quantitative metabolic studies is described.

The apparatus consists of a culture tube, a gas-distributing system, a mechanical rocker and a water bath of constant temperature.

The procedure consists in placing a lens aseptically in a sterile culture tube containing 4 or 5 ml. of bathing solution and incubating at constant temperature for any desired period. The bathing solution is changed at suitable intervals—for example, every twenty-four hours. A moist gas mixture is continuously passed over the bathing fluid, which is gently agitated throughout the period of culture.

Rabbit lenses cultured for fifteen days remained essentially transparent. A gradual decrease in the consumption of dextrose and the production of lactic acid was observed in two kinds of synthetic mediums and also in slightly modified beef aqueous humor. Loss of glutathione and ascorbic acid from the lens occurred over the course of several days of incubation, the former being greater in the absence of amino acids. Possible explanations of the altered metabolism are suggested, and the usefulness of this method for studying the metabolism of the lens is indicated.

CYCLOPIA WITH COMPLETE SEPARATION OF THE NEURAL AND MESODERMAL ELEMENTS OF THE EYE

Report of a Case

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AND
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NEW ORLEANS

NO STATEMENT regarding the incidence of cyclopia can be found in the literature despite the report of many cases over a long period of time. The specimen described in this paper represents the second case recorded at Charity Hospital, New Orleans, among 78,772 births during the period from 1938 through 1949.

The purpose of this paper is to present an anatomic study of a case of cyclopia showing fairly normal development of the orbit and sclera, though these structures were separated from the neural elements of the eye. These features have not previously been recorded in the literature.

HISTORICAL REVIEW

The literature dealing with cyclopia is extensive and will not be surveyed in detail. The principal theories regarding this anomaly may be summarized as follows:

1. Fusion of two originally separate eyes due to arrest or retardation of growth (Meckel,[1] 1826).

2. Persistence of a single vesicle (Huschke,[2] 1832.).

3. Arrest of development at an early phylogenetic stage (Kundrat,[3] 1872; Naegeli,[4] 1897).

From the Department of Pathology, Louisiana State University School of Medicine, and the Charity Hospital of Louisiana.

1. Meckel, J. F.: Ueber die Verschmelzungsbildungen, Arch. f. Anat. u. Physiol. **1**:238-310, 1826.

2. Huschke, E.: Ueber die erste Entwicklung des Auges und die damit zusammenhangende Cyklopie, Arch. f. Anat. u. Physiol. **6**:1-47, 1832.

3. Kundrat, V., in Schwalbe, E.: Die Morphologie der Missbildungen des Menschen und der Tiere, Jena, Gustav Fischer, 1909-1913, vol. 3, pt. 1, pp. 205-206.

4. Naegeli, O.: Ueber eine neue, mit Cyclopie verknüpfte Missbildung des Centralnervensystems, Arch. f. Entwcklngsmechn. **5**:168-218, 1897.

4. Defects in one or more of the organizers in the anterior end of the neural plate which determine the development of the eye (Spemann and associates,[5] 1901, 1918, 1927; Stockard,[6] 1909; Petersen,[7] 1923; Adelmann,[8] 1929).

5. Growing point theory. Cyclopia is considered to result from arrest or retardation in the growth of cells in the midline which normally separate the two eyes (Adami and McCrae,[9] 1912; Hill,[10] 1920; Keen,[11] 1946).

At present, most workers accept the view that in the orderly development of the embryo certain groups of cells (*Anlagen*) differentiate into masses destined to give rise to definite organs or tissues, and that injury or abnormality of these specialized cell masses at certain critical stages in their development can result in congenital malformation of these organs or tissues. Most of the controversy has revolved around the relative effects of heredity (genes) and environment (nutritional disturbances, physical agents, anoxia and infections). The recent demonstration of congenital malformations, including anomalies of the crystalline lens, e. g., cataract, associated with rubella in the first trimester of pregnancy (Gregg,[12] 1942; Cordes and Barber,[13] 1946), has shifted emphasis to acquired factors, and this shift in emphasis seems to be particularly appropriate in a condition incompatible with viability (and thus not directly inheritable), such as cyclopia.

It is safe to say that the cause of cyclopia has not been established. The two chief mechanisms are defective inheritance and unfavorable environment, both of which may be varied in innumerable ways. Thus, cyclopia may and does result from any deleterious agent acting on the embryo at or before final determination of the eye anlage, and after-

5. Spemann, H.: Ueber Correlationen in der Entwicklung des Auges, Verhandl. d. anat. Gesellsch. **15**:61-79, 1901; Ueber die Determination der ersten Organanlagen des Amphibienembryo, Arch. f. Entwcklngsmechn. **43**:448-555, 1918. Spemann, H., and Bautzmann, E.: Ueber Regulation von Tritonkeimen mit überschussigem und fehlendem medianem Material, ibid. **110**:557-577, 1927.

6. Stockard, C. R.: The Artificial Production of One-Eyed Monsters and Other Defects, Which Occur in Nature, by the Use of Chemicals, Anat. Rec. **3**:167-173, 1909.

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10. Hill, E.: Cyclopia: Its Bearing upon Certain Problems of Teratogenesis and of Normal Embryology, Arch. Ophth. **49**:597-620 (Nov.) 1920.

11. Keen, J. A.: A Note on the Morphology of Certain Congenital Malformations of the Head, Clin. Proc. **4**:325-334, 1946.

12. Gregg, N. M.: Congenital Cataract Following German Measles in Mother, Tr. Ophth. Soc. Australia **3**:35-46, 1942.

13. Cordes, F. C., and Barber, A.: Changes in Lens of Embryo After Rubella, Arch. Ophth. **36**:135-140 (Aug.) 1946.

ward by altering the interaction between the anlage and the surrounding endomesoderm. This action must take effect before the first manifestation of its bilateral nature—in the human embryo, at the 1.8 mm. stage (Jordan and Kindred[14]).

REPORT OF CASE

Clinical Record.—The specimen was the body of a Negro girl weighing 1,150 Gm. and measuring 14 cm. from crown to rump and 22 cm. from crown to heel. The infant was born at term, after a four hour labor induced with alpha-hypophamine (pitocin®). The presentation was cephalic (vertex); the position, left occipitoanterior, and delivery was spontaneous. The child died twenty minutes

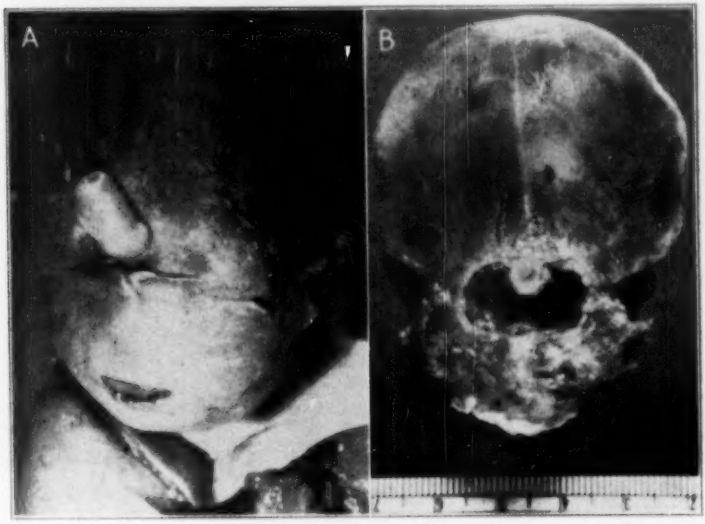

Fig. 1.—*A*, cyclopic monster; *B*, frontal bones united by midline suture, which extends from the superior margin of the median orbit to the anterior point of the bregmatic fontanel. The base of the proboscis is seen partially dividing the orbit.

after delivery, and congenital anomalies thought to be incompatible with life were noted by the attending physician.

The mother of the child was referred to Charity Hospital from an outlying parish with a diagnosis of toxemia of pregnancy.[15] Further clinical history furnished by her physician indicated that she had had toxemia and convulsions during

14. Jordan, H. E., and Kindred, J. E.: Textbook of Embryology, ed. 5, New York, D. Appleton-Century Company, Inc., 1948.

15. The obstetrics service of Dr. Curtis Lund and the pediatrics service of Dr. Myron Wegman, of the Charity Hospital of Louisiana, made available the clinical records in this case.

her first pregnancy, six years previously. The child was born at term, however, and was still living. The second pregnancy was also terminated at the end of nine months by spontaneous delivery, but the child lived only five minutes. There was no record of abnormalities in these children.

The clinical history stated that the mother had had high blood pressure for the past six years, or since her first pregnancy. Other pertinent laboratory data were as follows: negative serologic reactions; specific gravity in the Fishberg concentration test, 1.020; clearance in the phenolsulfonphthalein test, 55 per cent in two hours, and reaction of the urine for albumin, 2 plus. There was no history of infectious disease or other illness during gestation.

Necropsy diagnoses were (1) cyclopia, (2) biscuspid aortic valve, (3) high intraventricular septum defect and (4) cysts in the spleen.

Autopsy.—General Examination: The head was small but well shaped (fig. 1*A*). The buccal orifice was in its normal anatomic position and contained a well developed tongue. The oropharynx was normal, and a glottis was visualized;

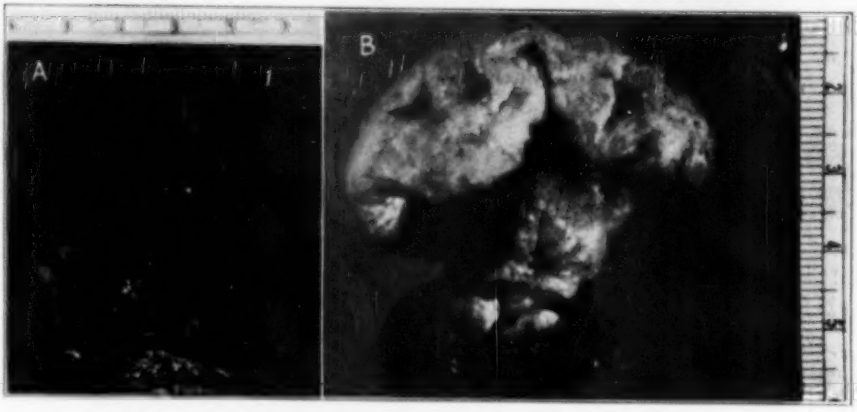

Fig. 2.—*A*, dorsal surface of the brain and large dorsal cyst; *B*, dorsal surface of the brain after removal of the cyst.

however, the epipharynx formed a blind pouch 7 mm. in depth, the oral aperture of which measured 10 by 3 mm. The single median orbit was covered with upper and lower eyelids, which presented a crease and an indentation, or notch, in the midline. A proboscis, measuring 21 mm. in length and 6 mm. in diameter and containing a single pinpoint orifice, was attached to the superior aspect of the orbit.

Brain and Cranial Contents: The frontal bone (fig. 1*B*) presented a midline suture, extending from the superior margin of the median orbit to the anterior point of the very small bregmatic fontanel. The inner surface of these bones showed two large frontal fossae but no frontal sinuses.

Figure 2*A* shows the dorsal surface of the brain and the large cyst, and *B*, the same surface after removal of the dorsal cyst. The cerebrum was not divided into hemispheres, and the sulci and gyri were not as prominent or as clearly marked as in the case of a normal brain at term. The frontal lobes of the cerebrum appeared to be pushed medially and partially covered by the relatively large

temporal lobes. The circle of Willis was encountered immediately beneath the frontal lobes, so that, while the anterior and middle cerebral vessels were in proper relation to each other, they were far rostral to their normal position. No evidence could be found that the olfactory bulbs or tracts had ever existed. A search for the

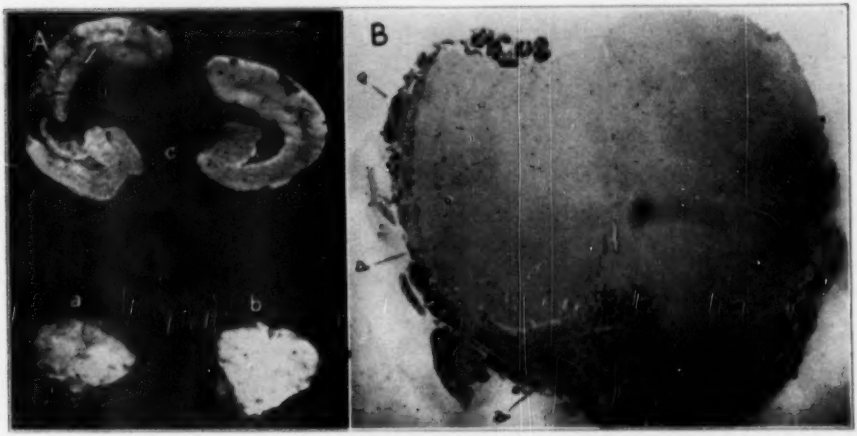

Fig. 3.—*A*, coronal sections of the brain: *a* and *b*, through the thalamus; *c*, through the caudal end of the cerebrum. *B*, microscopic section through the thalamus (coronal section *A*, *b*), showing attachment (*a*) of the dorsal cyst as an angiomatous extension, with no septum or capsule separating it from the neural tissue.

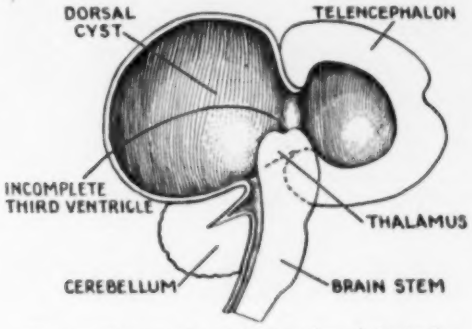

Fig. 4.—Diagram of a sagittal section of the brain.

optic nerves, optic chiasm, optic tracts and infundibulum failed to reveal these structures.

Coronal sections were made of the brain and brain stem. Sections of the caudal end of the cerebrum and the thalamus are shown in figure 3. No midline dividing

structures, such as the corpus callosum or the septum pellucidum, or any communications, such as the foramens of Monro or the anterior and posterior commissures, could be identified.

The common ventricle of the telencephalon was not divided into distinct lateral ventricles but formed a large, horseshoe-shaped space, which opened posteriorly

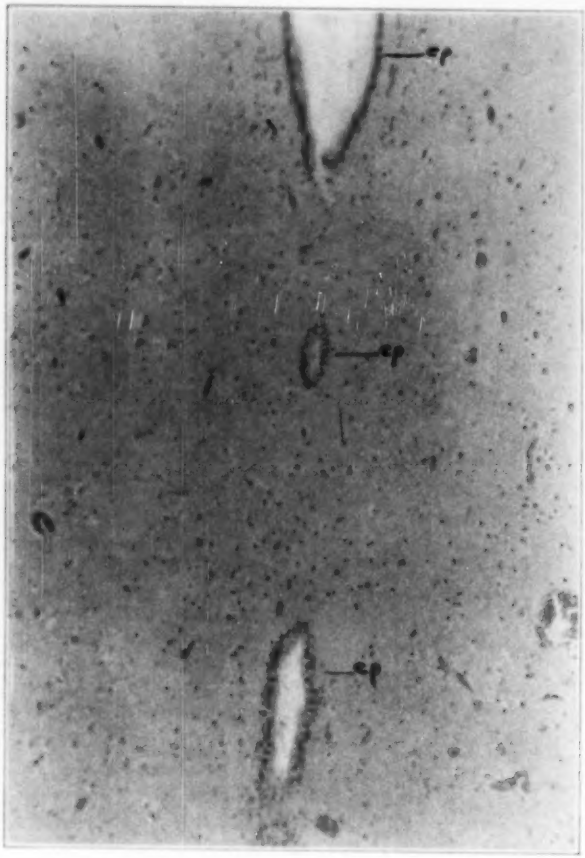

Fig. 5.—Microscopic section showing linear row of ependymal rosettes (*ep.*), which constitute the caudal end of the third ventricle.

into the dorsal cyst. The communication between the dorsal cyst and the third ventricle was seen between the two thalami. The aqueduct of Sylvius was not found. The fourth ventricle appeared to be normal in its relation to the brain stem.

Some resemblance could be seen to a cornu ammonis bilaterally in the posterior superior portion of the cerebrum; however, no insular formation was developed.

Sections through the diencephalon showed increased vascularity similar to that noted in the sections of the cerebrum. The cerebellum, on the other hand, contained gross hemorrhages between the septums.

Figure 4 is a diagrammatic representation of the relation of these structures, as seen on gross examination.

Microscopic Study and Interpretation of the Brain.—A detailed description of the various sections of the cerebrum and cerebellum is not applicable to this paper. Only our interpretation of the gross and microscopic observations, together with selected illustrations, is presented.

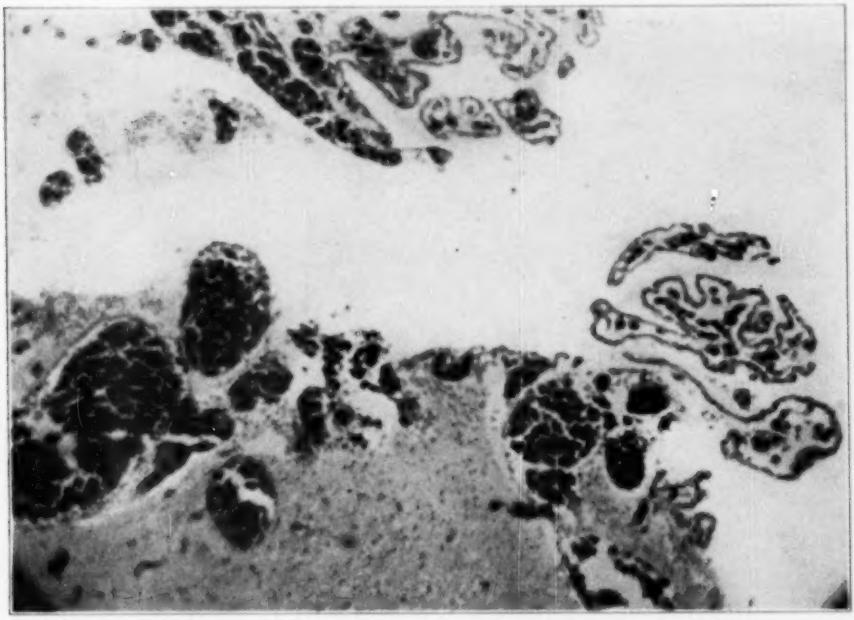

Fig. 6.—Mass of choroidal material on the external surface of the brain at the level of the thalamus.

The entire brain was fixed in a neutral solution of formaldehyde U. S. P. (1:4), and coronal sections were cut. Blocks of tissue were taken from the larger coronal sections, but the smaller ones were prepared whole. Serial sections were stained by various histologic technics and by the prussian blue method for iron.

Histologically, the entire brain presented the picture of retarded development. The normal arbor vitae arrangement of the folia of the cerebellum was represented by unbranched, digitate processes. The nuclei globosi and nuclei dentati, as well as the nuclear layers, were in an early stage of differentiation. The mesencephalon was represented only by the poorly developed cerebral peduncles and the ventral portion of the pons. The two underdeveloped thalami were the only recognizable structures derived from the diencephalon, and these formed the floor of the dorsal

cyst. Retarded development was further evident in the fact that the cerebrum was not divided into hemispheres and that none of the dividing or communicating structures in the midline were present. The cerebral cortex was not divided into sulci or gyri, and histologically it presented the primitive arrangement of ependymal, mantle and marginal layers. The rhinencephalon and pars optica were absent, and the myelination normally seen at birth could not be demonstrated by the usual methods.

The large dorsal cyst located between the cerebrum and the cerebellum was interpreted as the evaginated choroid plexus. This diagnosis was supported by the

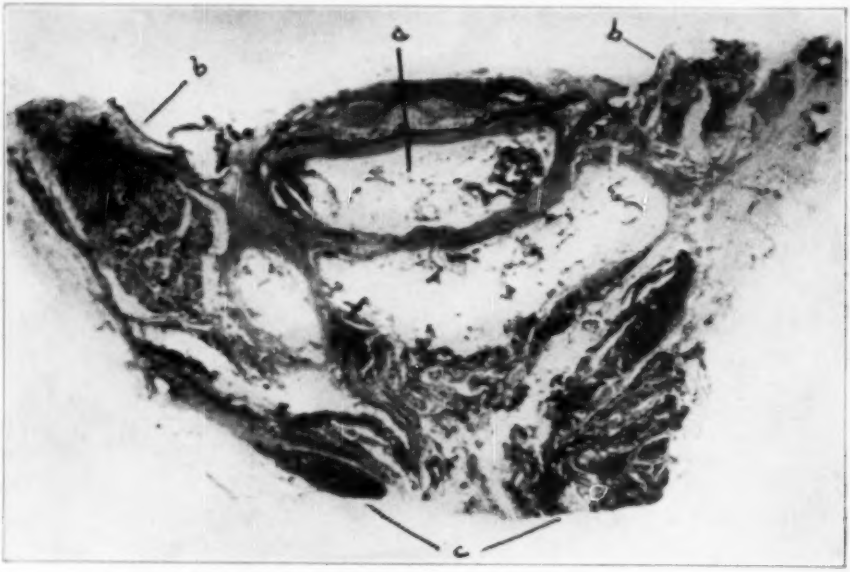

Fig. 7.—Horizontal section through orbital contents: (*a*) scleral sac; (*b*) lacrimal glands; (*c*) muscle crescent.

presence of small masses of tela choroidea on the external surface of the brain (fig. 6). Its ventroinferior attachment could be seen as a fibrous, angiomatous projection, or pedicle, which extended into the substance of the brain, with no evidence of a septum or capsule separating it from the neural tissue (fig. 3*B*). The cavity of the cyst communicated with the common ventricle of the telencephalon medium, anteriorly, and with the fourth ventricle, posteriorly. Thus, circulation of fluid was possible, and hydrocephalus did not occur in spite of occlusion of the posterior portion of the third ventricle (fig. 5) and obliteration of the aqueduct of Sylvius.

The striking increase in vascularization of the whole brain, the meninges and the walls of the dorsal cyst appeared to have resulted from stimulation and over-

growth of mesoderm. Hemorrhage and stasis had been followed by the presence of amorphous masses of material, which had the histologic characteristics of calcium and were interpreted as degenerative products.

Orbital Contents.—Grossly, the orbital contents formed a triangular mass of tissue, in which no ocular structures, such as the cornea or iris, could be seen. The orbit presented the appearance of fusion of the temporal halves of two orbits (fig. 1*B*). A proboscis, measuring 21 mm. in length and 6 mm. in diameter, was attached by a cartilaginous plate to the superior aspect of the roof of the orbit.

Microscopic examination revealed that the anterior portion of the orbital mass contained two well developed lacrimal glands, which occupied the superior temporal quadrant bilaterally (fig. 7). The center of the mass contained a saclike structure,

Fig. 8.—Microscopic section of bone from the floor of the orbit: (*a*) neural portion of eye; (*b*) loose mesodermal tissue; (*c*) bone.

which was incomplete in the upper part, where the proboscis was situated, and partially double in the inferior half, where it was incompletely bisected by horizontal muscle fibers and mesodermal elements. Compact collagenous cells, resembling scleral tissue, composed the wall of the sac, which was filled with fatty tissue containing two large blood vessels. The lower half of this scleral sac was partially enclosed in a crescent composed of four large muscles. These muscles took origin from the bones at the apex of the orbit and could be traced to the anterior segment of the scleral sac. The tip of the muscle crescent contained a single large nerve, which was enclosed in a connective tissue sheath. This nerve branched immediately inside the orbit and terminated in relation to the aforementioned muscles. It was interpreted as a motor nerve.

The soft tissue and bone taken from the floor of the orbit at its apex contained the neural elements of an eye (fig. 8). The scattered glial tissue appeared to be surrounded by loose mesodermal elements and was cradled in well developed bone. Pigment epithelium could be identified, and adjacent to it were rosettes which resembled retinal cells of the third and fourth fetal months. These cells were uniform in size and shape and were arranged in a circle (fig. 9). A delicate internal limiting membrane could be discerned with fine, cilia-like processes extending into the lumen. These rosettes were similar to the rosettes found in a retinoblastoma. The retinal architecture was greatly disorganized, and several large amorphous masses, which stained dark blue with hematoxylin, were present

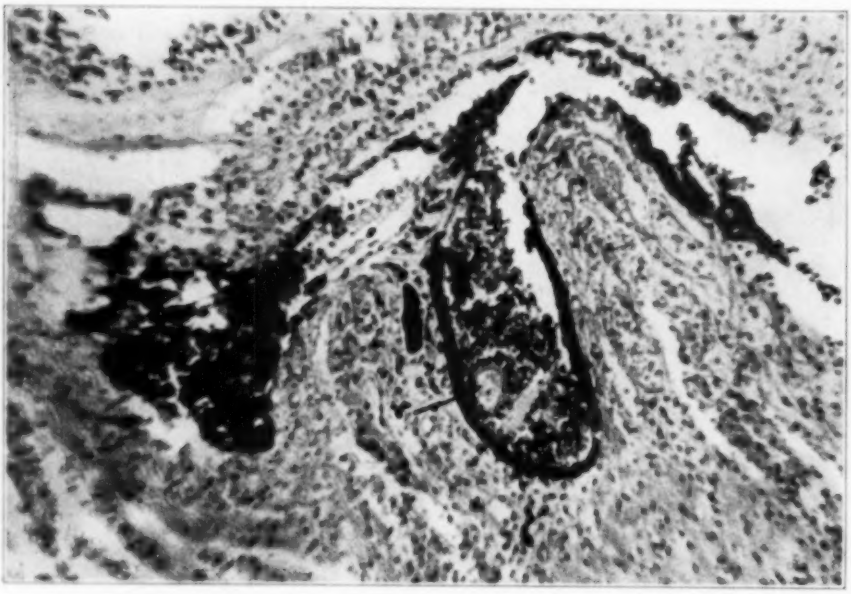

Fig. 9.—High power magnification of section in figure 8, showing pigment epithelium and retinal tissue (r).

among the glial cells. No ganglion cells or nerve fibers could be identified among the retinal elements. The anterior lobe of the hypophysis (fig. 10) was located anterior to the neural portion of the eye, but on a lower level, in the soft infra-orbital tissues, and was enclosed on three sides by the body and the processes of the sphenoid bone. No connection remained between the anterior lobe of the hypophysis and the blind epipharynx. The glandular nature of this organ was apparent. It was composed of chromophobic and eosinophilic cells interspersed in a delicately interlacing connective tissue stroma. Numerous small blood vessels penetrated its substance.

The posterior lobe of the neurohypophysis, as such, could not be identified.

Interpretation of the Eye and Orbit.—Incarceration of the neural elements of the eye, i. e., the retina and retinal epithelium, in the nasoethmoidal bone formation beneath the median orbit is of unusual importance in estimating the time and spatial relation of the structures involved in this case.

The single condition of the pars optica places the time of the initial injury at a very early stage of development, probably the embryonic plate stage. Bilateral optic sulci appear in the anterior end of the neural tube about the beginning of the third week, or the 1.8 mm. stage (Jordan and Kindred[14]), before the anterior neuropore closes. Thus, the retarding influence must have occurred prior to this stage.

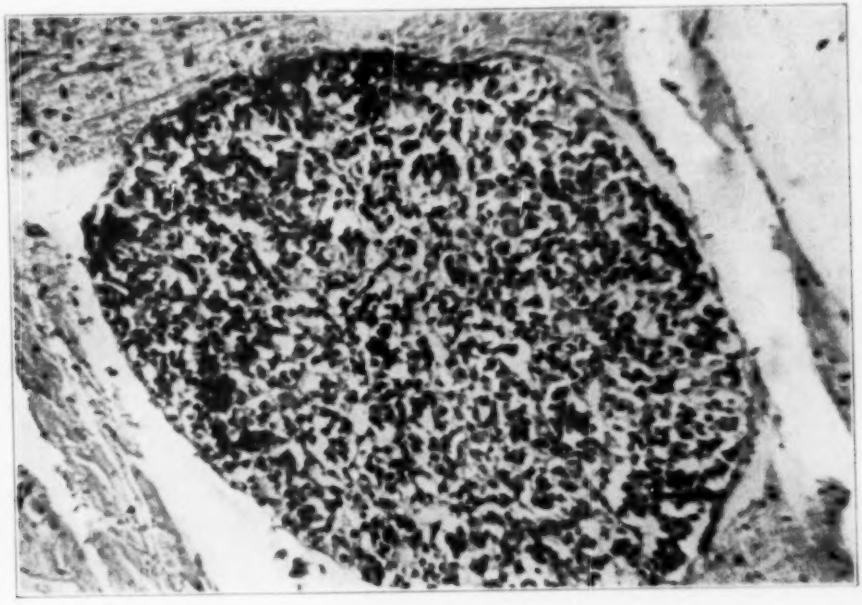

Fig. 10.—Anterior lobe of the hypophysis.

The total absence of a lens indicates that the retarded rate of growth of the neural ectoderm prevented its contact with the surface ectoderm. Normally the lens develops from surface ectoderm in close association with the neural ectoderm, and its development may be dependent on this association (Spemann,[16] Mann[17]) during the third week, approximately at the 3 to 4 mm. stage, when the optic

16. Spemann, H.: Ueber Linsenbildung bei defecter Augenblase, Anat. Anz. **23**:457-464, 1903.

17. Mann, I. C.: Development of the Human Eye, London, Cambridge University Press, 1928; Developmental Abnormalities of the Eye, London, Cambridge University Press, 1937.

vesicle approaches the surface ectoderm. This stage in the development of the eye did not occur.

The stage of differentiation of the retinal elements, however, appeared to be equivalent to that of the third or fourth fetal month, but no ganglion cells or nerve fibers were present. Thus, while the growth rate of the anterior end of the neural tube was slower than normal, and slower than the adjacent mesoderm, development was not completely arrested. The absence of the optic nerve, optic chiasm and optic tracts can be explained by failure of the ganglion cells to become differentiated. It is known that the primordia of these structures will degenerate unless penetrated by the axons of the ganglion cells (Gruenwald[18]).

The altered growth rate is further emphasized by the precocious development of all the mesodermal derivatives of the face and head. Retardation in the growth of neural tissue or acceleration in the growth rate of the mesodermal tissue had involved the posterior portion of the pituitary gland, which was prevented from coming in contact with the ectodermal portion, or Rathke's pouch. Some differentiation of the hypophysis, however, had occurred, and the structure resembled the stage of development seen during the third or fourth fetal month.

Isolation of the neural elements from the mesodermal elements of the eye indicates that the influence of neural tissue on mesodermal tissue was negative, since no orbital architecture was evident in relation to the retinal elements. On the other hand, the stimulus to form an orbit could be expressed by the mesoderm independently of the neural influence. This independence of mesodermal tissue extended to the sclera of the eye.

An indication of bilateral symmetry could be seen in the mesodermal structures, namely, the orbits, lids, muscles and scleras. This is additional evidence that the retarding influence did not arise in the mesoderm and that the distortion of the structures of mesodermal origin was due to abnormal spatial relations.

COMMENT

Experimental embryology has shown that cyclopia results from an arrest in development of the anterior end of the neural plate, and that it does not necessarily imply the absence of eye-forming material. If one accepts the view that the anlage of the eye is centrally placed in the medullary plate stage and that it divides and migrates bilaterally, establishing two physiologic centers of growth at the neural plate stage, then an arrest in development previous to this division must result in a single median eye, or cyclopia.

It seems impossible that a normal forebrain could be formed in the presence of such a major defect, and no instances have been recorded except of those produced experimentally in fish embryos (Stockard[6]). Thus, cyclopia is always associated with abnormalities of the brain, the most frequent being telencephalon medium, in which there is no division into cerebral hemispheres, and a dorsal cyst. For this reason, we question Blanc's[19] classification, in which reduction of the face

18. Gruenwald, P.: Absence of the Optic Nerve in Cyclopia, Anat. Rec. **91**:13-20, 1945.

19. Blanc, L.: Otocéphalie et cyclopie, J. de l'anat. et de physiol. **31**:187-218 and 288-309, 1895.

with approach of the ears and cyclopia are placed in a group characterized by a well formed brain. On the other hand, these same abnormalities of the brain may occur without cyclopia and must result from arrests occurring slightly later than that causing cyclopia. In the case reported by de Lange [20] the specimen possessed two eyes and two optic nerves with an undivided forebrain, which, however, showed slight bilateral protuberances of the common ventricle of the telencephalon. In her case, also, there was complete absence of the olfactory bulbs and tracts, but the nose was normal in position and showed only a minor defect. Her case was well documented, and one is tempted to postulate that the arresting influence occurred after the appearance of the optic vesicles, and before the appearance of the cerebral hemispheres, and that an arrest resulting in cyclopia must occur in an earlier stage of development than one involving the rhinal apparatus alone. It follows that an earlier arrest involves more neural material, since cyclopia is almost invariably associated with defects of the rhinal apparatus and the forebrain. It would seem, therefore, that if two physiologic growth centers had been established in bilateral eye areas in de Lange's case, a later central defect must have occurred which spared the already developing eyes and affected only the brain and the olfactory apparatus.

The other abnormality of the brain frequently associated with cyclopia is a large dorsal cyst, usually located between the undivided telencephalon and the cerebellum. It varies in size and in its relation to the surrounding structures; however, most observers agree that its walls are thick and vascular and that the walls appear to be a direct continuation of the cortical wall. In Mettler's [21] case it was approximated to and fused with the dorsal surface of the thalamus, sealing over the third ventricle. In the case reported by Black [22] the dorsal cyst was not described as such, but his illustrations show a membranous roof attached to the inner surface of the telencephalon medium which seems to us to represent a variation in the formation of the cyst. De Lange [20] stated the belief that the dorsal cyst represented the roof of the third ventricle turned inside out. Winkler [23] described such a cyst in 2 specimens of cyclopia in man, in 2 specimens of cyclopia in calves and in 1 specimen of cyclopia in a pig, and stated that the cyst in those cases represented the evaginated roof of the mesencephalon.

20. de Lange, C.: Cebocephalia minor (Beitrag zur Kenntnis der Cyclopien), Acta psychiat. et neurol. **15**:299-336, 1940.

21. Mettler, F. A.: Congenital Malformation of the Brain, J. Neuropath. & Exper. Neurol. **6**:98-110, 1947.

22. Black, D. D.: The Central Nervous System in a Case of Cyclopia in Homo, J. Comp. Neurol. **23**:193-257, 1913.

23. Winkler, H.: The Brain in a Case of Cyclopia Incompleta, Folia neurobiol. **10**:105, 1916.

In our case, the dorsal cyst communicated anteriorly with the cavity of the telencephalon and posteriorly with the fourth ventricle and was attached around the base of the thalamic mass. The tela choroidea could not be found inside the common ventricle of the telencephalon, the remnant of the third ventricle or the dorsal cyst, but masses were noted on the external surface. It is our opinion that the dorsal cyst represents a much altered material, which in normal development would have formed at least part of the tela choroidea. The brain as a whole showed retardation in development and cellular differentiation.

The neural elements of the eye appeared to be affected by the same retarding influence as that acting on the neural tissue in general. The ability of the organism, however, to readjust to the altered spatial relations and interactions of misplaced tissues is more clearly demonstrated by the condition of the eye. In the present case the normal interaction between the neural elements and the mesodermal elements of the eye was prevented by separation of the optic vesicle from the brain and its incarceration in the bone formation beneath the orbit. Nevertheless, a fairly well formed orbit and sclera developed without the influence of the optic vesicle. Although the orbit consisted of a single cavity, there was ample evidence of its inherent bilateral nature. The outer rim formed a bilobed, or figure 8, aperture, and an indentation, or notch, was visible in the upper and lower eyelids. The scleral sac within the orbit contained an incomplete septum, which was interrupted by the attachment of the proboscis. Many cases of anophthalmos have been reported in which the orbit was normally developed in the complete absence of an optic vesicle (Mann [13]). A careful search of the literature, however, has failed to reveal the formation of a sclera inside the orbit in such cases. In contrast to the independence exhibited by the development of the mesodermal derivatives, the absence of the lens indicates the inability of the surface ectoderm to form this structure apart from the retina.

It is our opinion that the condition of the eye indicates the probable course of events in this case. The single condition of the optic vesicle indicates that the arrest in development occurred before the appearance of the bilateral optic sulci, probably before the 1.8 mm. stage.

In normal development the optic sulci have evaginated to form optic vesicles by the 4 mm. stage (Jordan and Kindred [14]). At this time a thin layer of mesoderm surrounds the forebrain and optic vesicles except at the distal ends of the vesicles and immediately below the forebrain in the middle line, where Rathke's pouch will develop. The lens is developed from the surface ectoderm at its point of contact with the optic vesicle. In our case the single optic vesicle was prevented from coming into contact with the surface ectoderm by the ingrowth of mesoderm, so that no lens was formed.

Whether the undue ingrowth of mesoderm can be interpreted as indicating an acceleration in the rate of growth of the mesoderm, or whether it is only relative to the retardation of the neural tissue, is impossible to say. There is a striking contrast, however, between the precocious differentiation of the mesodermal derivatives and the development of structures of neural origin. This is further evidence by the isolation of the anterior lobe of the hypophysis and its incarceration in the bones beneath the brain. The neural derivatives, on the other hand, showed a decided retardation in development and in cellular differentiation.

CONCLUSIONS

An unusual case of cyclopia, with separation of the neural and mesodermal elements of the eye, is described. The separate development of these two primitive tissues is interpreted as showing the independence of development of the mesoderm of the eye and that of the orbit.

The total absence of the lens tends to confirm the hypothesis that the normal development of this structure, in certain species, is dependent on contact of the neural and the surface ectoderm.

The retardation in development of the eye and brain was general and could be oriented in time. The cellular differentiation of the retina, the brain and the anterior lobe of the hypophysis was estimated to be that usually described for the third or fourth fetal months. It is possible that this lag in development of the neural tissue had resulted in the formation of a large dorsal cyst by the evagination of that part of the primitive brain wall which normally forms tela choroidea.

The main theories of causation of anomalies of the anterior end of the central nervous system are reviewed and correlated with the findings in the present case. We believe that the initial deviation from normal development occurred during the neural plate stage, or at about 1.8 mm. length, before the optic sulci were formed, and was followed by retarded development of the neural ectoderm and/or accelerated growth of the mesoderm.

No etiologic factor was clearly evident in this case. Maternal hypertension was considered but was deemed improbable.

No reliable estimate of the incidence of cyclopia can be found, and this case represents the second in a series of 78,772 births during the twelve year period of 1938 through 1949 at Charity Hospital.

Louisiana State University.

CHOLINESTERASE ACTIVITY IN OCULAR TISSUES AND FLUIDS

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NEW YORK

BECAUSE of recent advances in the knowledge of the functional importance of cholinesterase, it was considered advisable to investigate this enzyme from the ophthalmologic point of view. The purpose of this paper is to review the literature and to present new experimental data on the activity of cholinesterase in various ocular tissues and fluids, both in the experimental animal and in man.

I. REVIEW OF THE LITERATURE

A. GENERAL LITERATURE

Since Loewi's [1] fundamental discovery in 1921 of a parasympathomimetic substance in the perfusion fluid passed through a dog's heart, literally thousands of papers have been published pertaining to this parasympathomimetic substance—acetylcholine—and its specific enzyme, cholinesterase. The existence of such an enzyme was first demonstrated by Loewi and Navratil,[2] and the Stedmans,[3] in 1932, gave it the present name of cholinesterase. The most important chemical and physiologic characteristics of cholinesterase have been well summarized in several review articles recently published by Nachmansohn [4] and in Augustinsson's [5] monograph. They are as follows:

1. The enzyme is universal in the conductive tissues (muscle and nerve) of practically the entire animal kingdom. 2. It is present in high

Supported by the Knapp Memorial Foundation.

From the Department of Ophthalmology, Columbia University College of Physicians and Surgeons, and the Institute of Ophthalmology, Presbyterian Hospital.

1. Loewi, O.: Ueber humorale Uebertragbarkeit des Herznervenwirkung, Arch. f. d. ges. Physiol. **189**:239, 1921.

2. Loewi, O., and Navratil, E.: Ueber humorale Uebertragbarkeit des Herznervenwirkung: X. Ueber das Schicksal des Vagusstoffes, Arch. f. d. ges. Physiol. **214**:678, 1926.

3. Stedman, E.; Stedman, E., and Easson, L.: Choline-Esterase: An Enzyme Present in the Blood Serum of the Horse, Biochem. J. **26B**:2056, 1932.

4. Nachmansohn, D.: (*a*) On the Physiological Significance of Choline-Esterase, Yale J. Biol. Med. **12**:565, 1940. (*b*) Role of Acetylcholine in the Mechanism of Nerve Activity, Vitamins & Hormones **3**:337, 1945. (*c*) Chemical

enough concentrations in the nerve tissue to hydrolyze the amount of acetylcholine formed during nerve conduction. 3. This hydrolysis takes place at an extremely rapid rate; the "turn-over number" of cholinesterase is estimated to be about 20,000,000 per minute. 4. It is localized at the neuronal surfaces, where the biochemical and electrical phenomena take place. 5. The esterase in muscle and nerve is specific for acetylcholine, in contrast with the so-called nonspecific esterase found in other organs and tissues, such as the blood serum, liver, pancreas and kidney. This specificity is only relative, but it is distinctive enough to be a good differentiating factor. 6. There is a direct proportionality between the action potential and the cholinesterase activity, as demonstrated in the electric organ of the electric eel. 7. Certain anticholinesterase agents inhibit, and in sufficiently high concentrations irreversibly abolish, the action potential. The degree of inhibition of the action potential by these drugs is directly proportional to the degree of inhibition of the enzyme, as shown by biochemical methods.

On experimental evidence obtained from studies on cholinsterase, the chemical transmission theory of nerve conduction was postulated by Dale and his associates.[6] According to this theory, acetylcholine is produced at the nerve ending by the arrival of the nerve impulse and, after acting directly on the muscle fiber at its end plate, is destroyed during the refractory period by a high local concentration of cholinesterase.

Contrary to this point of view is the so-called conductivity theory of Nachmansohn.[7] During the course of his extensive biochemical and

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Mechanism of Nerve Activity, Ann. New York Acad. Sc. **48**:395, 1946. (*d*) Chemical Mechanism of Nerve Action, in Green, D. E.: Currents in Biochemical Research, New York, Interscience Publishers, Inc., 1946, p. 335. (*e*) The Role of Acetylcholine in Conduction, Bull. Johns Hopkins Hosp. **83**:463, 1948.

5. Augustinsson, K. B.: Cholinesterases: A Study in Comparative Enzymology, Acta physiol. Scandinav. (supp. 52) **15**:1, 1948.

6. Dale, H., and Feldberg, W.: The Chemical Transmitter of Vagus Effects to the Thyroid, J. Physiol. **81**:320, 1934. Dale, H.: Pharmacology of Nerve-Endings, Proc. Roy. Soc. Med. **28**:319, 1935. Dale, H.; Feldberg, W., and Vogt, M.: Release of Acetylcholine at Voluntary Nerve Endings, J. Physiol. **86**:353, 1936. Dale, H.: Transmission of Nervous Effects by Acetylcholine, in Harvey Lectures, 1936-1937, Baltimore, Williams & Wilkins Company, 1937, p. 229. Physiology of the Nervous System, Science **90**:393, 1939.

7. Nachmansohn, D.: (*a*) Cholinestérase dans le tissu nerveux, Compt. rend. Soc. de biol. **127**:894, 1938; (*b*) Cholinestérase dans les tissus embryonnaires, ibid. **127**:670, 1938; (*c*) Cholinestérase dans le ganglion sympathique cervical supérieur du chat, ibid. **129**:830, 1938; (*d*) Distribution de la cholinestérase dans le cerveu humain, ibid. **128**:24, 1938; (*e*) Transmission of Nerve Impulses in the Central Nervous System, J. Physiol. **93**:2, 1938; (*f*) Cholinestérase dans le fibres nerveuses, Compt. rend. Soc. de biol. **128**:516, 1938; (*g*) Changements de la cholinestérase dans le muscle strié, ibid. **128**:599, 1938; (*h*) Choline Esterase in Voluntary Muscle, J. Physiol. **95**:29, 1939; (*i*) Choline Esterase in Brain and

(Footnote continued on next page)

biophysical investigations, this author showed that acetylcholine is produced and hydrolyzed not only at the synapse but also along the course of the whole nerve fiber. He therefore assumed that the role of acetylcholine at the synapse is the same as that in the axon. The rapid appearance and removal of acetylcholine cause depolarization of the surface membranes of the nerve cell. This depolarized region becomes negatively charged, and thus a flow of current occurs from here to the next point along the course of the nerve fiber. Here, again, acetylcholine causes depolarization, and the whole process is repeated. The same phenomenon takes place at the synapse. Thus, according to Nachmansohn's theory, the transmitting factor in nerve conduction, both at the synapse and along the nerve fiber, is the electric current, but this current is produced by the release of acetylcholine.

This theory is not universally accepted and has been criticized, notably by Eccles,[8] Lorente de Nó,[9] Koelle and Gilman,[10] Crescitelli and associates [11] and others.

B. OPHTHALMOLOGIC LITERATURE

As compared with the vast amount of literature concerning cholinesterase in general, the ophthalmologic literature is rather limited. In the following review an attempt is made to cover all the literature extant related to studies on cholinesterase in the eye.

Cornea.—Brucke and associates [12] noted more cholinesterase activity in the epithelium than in the stroma of the cornea of the normal rabbit.

Spinal Cord of Sheep Embryos, J. Neurophysiol. **3**:396, 1940. (*j*) Nachmansohn, D.; Coates, C., and Cox, R.: Electric Potential and Activity of Choline Esterase in the Electric Organ of Electrophorus Electricus (Linnaeus), J. Gen. Physiol. **25**:75, 1941. (*k*) Nachmansohn, D., and Meyerhof, B.: Relation Between Electrical Changes During Nerve Activity and Concentration of Choline Esterase, J. Neurophysiol. **4**:348, 1941. (*l*) Nachmansohn, D.; Coates, C., and Rothenberg, M.: Studies on Cholinesterase: II. Enzyme Activity and Voltage of the Action Potential in Electric Tissue, J. Biol. Chem. **163**:39, 1946. (*m*) Nachmansohn, D., and Rothenberg, M.: Difference Between Pharmacological Action and the Physiological Role of Acetylcholine, Federation Proc. **7**:84, 1948.

8. Eccles, J.: Acetylcholine and Synaptic Transmission in the Spinal Cord, J. Neurophysiol. **10**:197, 1947; Conduction and Synaptic Transmission in the Nervous System, Ann. Rev. Physiol. **10**:93, 1948.

9. Lorente de Nó, R.: Quaternary Ammonium Ions and Sodium Ions in Nerve Physiology, Bull. Johns Hopkins Hosp. **83**:497, 1948.

10. Koelle, G., and Gilman, A.: Anticholinesterase, Drugs, Pharmacol. Rev. [1]: 166, 1949; in J. Pharmacol. Exper. & Therap. **95** (April, pt. 2):166, 1949.

11. Crescitelli, F.; Koelle, G., and Gilman, A.: Transmission of Impulse in Peripheral Nerves Treated with Di-Isopropyl Fluorophosphate, J. Neurophysiol. **9**:241, 1946.

12. Brucke, H.; Hellauer, H., and Unrath, K.: Azetylcholin und Aneuringehalt der Hornhaut und seine Beziehungen zur Nervenversorgung, Ophthalmologica **117**:19, 1949.

Aqueous.—Weve and Fischer[13] and Uvnäs and Wolff[14] could measure no cholinesterase activity in the aqueous of the horse or ox eye; however, if the enucleated ox eye was kept in the refrigerator for five to six hours and/or the secondary aqueous was tested, the sample of the first paracentesis being discarded, Uvnäs and Wolff found some cholinesterase activity in the bovine aqueous. They stated the belief that in the course of postmortem changes the biologic barriers are broken down and thus some enzyme finds its way into the anterior chamber, and, further, that partial emptying of the anterior chamber causes inflow of fluid from the surrounding tissues, e. g., the vitreous and iris. Jaffe[15] reported similar results; cholinesterase activity was pronounced in the secondary aqueous of the cat, but it was absent in the primary aqueous. No cholinesterase activity was found by Plattner and Hintner[16] in the rabbit aqueous, and similar negative results were noted by Engelhart[17] for the aqueous of the normal cat and rabbit eyes; however, when the eyes of rabbits were treated with physostigmine prior to puncture of the aqueous, some degree of acetylcholine-like response was noted in the aqueous. Small, but definite, amounts of cholinesterase were demonstrated by Brückner[18] in the aqueous of the horse and the ox. Velhagen[19] noted parasympathomimetic activity in the normal human aqueous, and Grosz and Goreczky[20] demonstrated an increased cholinesterase content in aqueous obtained from glaucomatous patients. A relative deficiency of parasympathomimetic activity in the aqueous of eyes with chronic simple glaucoma was reported by Bloomfield.[21]

13. Weve, H. J. M., and Fischer, F.: Ueber den Azetylcholinesterase-Gehalt der subretinalen Flüssigkeit bei rupturellen Netzhautablösungen, Ophthalmologica **96**:348, 1939.

14. Uvnäs, B., and Wolff, H.: About the Presence of Acetylcholine Esterase in the Aqueous Humor and the Vitreous Body of the Eye, Skandinav. Arch. f. Physiol. **77**:86, 1937; On the Occurrence of Acetylcholine Esterase in the Aqueous Humour and Vitreous Body, Acta ophth. **16**:157, 1938.

15. Jaffe, N.: Cholinesterase in the Aqueous of the Eye, Arch. Ophth. **40**:273 (Sept.) 1948.

16. Plattner, F., and Hintner, H.: Die Spaltung von Acetylcholin durch Organextrakte und Körperflüssigkeiten, Arch. f. d. ges. Physiol. **225**:19, 1930.

17. Engelhart, E.: Der humorale Wirkungsmechanismus der Oculomotoriusreizung, Arch. f. d. ges. Physiol. **227**:220, 1931.

18. Brückner, R.: Auge und Cholinesterase, Ophthalmologica, **105**:37, 1943; Vorkommen und Verteilung von Cholinesterase in der Uvea, ibid. **106**:200, 1943.

19. Velhagen, K.: Einleitende Untersuchungen über das Vorkommen aktiver und neurotroper Substanzen im Auge, Arch. f. Augenh. **103**:424, 1930; Ueber das Vorkommen depressorischer Substanzen im Auge, ibid. **104**:546, 1931; Zur Frage der Vagotropen Substanzen im Auge, ibid. **105**:573, 1932; Neue Untersuchungen über aktive Stoffe im Auge, ibid. **109**:195, 1936.

20. Grosz, T., and Goreczky, L.: Adatok a primaer glaucoma pathogenesisehez, Budapest, Szemeszeti Tanulmanyok, 1948.

21. Bloomfield, S.: Relative Deficiency of Parasympathomimetic Activity in Aqueous of Eyes with Chronic Simple Glaucoma, Arch. Ophth. **37**:608 (May) 1947.

Pletneva and associates [22] observed that the aqueous of 35 per cent of glaucomatous eyes examined showed an acetylcholine-like effect on the isolated frog heart preparation.

Vitreous.—Uvnäs and Wolff [14] and Weve and Fischer [15] reported measurable amounts of cholinesterase in the horse and ox vitreous, and the last-mentioned authors also noted the presence of this enzyme in human vitreous. Brückner [16] demonstrated cholinesterase activity in the vitreous of the horse, calf, ox and pig, the vitreous of the cow showing higher activity in the peripheral, marginal zone than in the central part; thus he concluded that the esterase in the vitreous probably originates from the retina.

Iris.—Bakker [23] and Plattner and Hintner [19] demonstrated cholinesterase activity in the rabbit iris, and considerable parasympathomimetic activity in the cat and rabbit iris was noted by Engelhart.[17] Armstrong [24] reported a high enzyme content of the sphincter pupillae of the turtle and only a trace in the amphibian sphincter pupillae. Brückner [16] made detailed studies on the various layers of the ox iris; he observed the highest cholinesterase activity in the pars pupillaris and lower values for the pigment epithelium, the pars intermedia, the entire iris and the pars ciliaris, in that order.

Ciliary Body and Choroid.—Engelhart [17] reported parasympathetic activity in the ciliary body of the cat and rabbit, and Velhagen [18] showed the same type of activity in extracts of the urea of the rabbit, sheep and ox. Bakker [23] demonstrated the presence of this enzyme in the rabbit's ciliary body, and Weve and Fischer [15] obtained similar results for the human choroid. It was shown by Herrmann and Friedenwald [25] that esterase activity was slightly higher in the stroma than in the epithelium of the ciliary body of beef and pig eyes. Using histochemical methods, Koelle and Friedenwald [26] demonstrated such activity in the ciliary body. Brückner, taking various parts of the ciliary body, showed increasingly high concentrations of cholinesterase in the stroma, ciliary processes and the ciliary muscle, in that order.

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22. Pletneva, N. A.; Raeva, N. V., and Voronina, E. G.: Biologische Analyse der Flüssigkeit aus der Vorderkammer der glaukomatösen Kranken, Vestnik. oftal. **13**:462, 1938; abstracted, Zentralbl. f. d. ges. Ophth. **43**:693, 1939.

23. Bakker, A.: Beiträge zur Kenntniss einiger merkwürdiger Pupillenbewegungen, Arch. f. Ophth. **139**:273, 1938.

24. Armstrong, P.: Cholinesterase in the Amphibian Sphincter Pupillae, J. Cell. & Comp. Physiol. **20**:47, 1942; Cholinesterase at the Nerve Termination in the Sphincter Pupillae of the Turtle, ibid. **22**:1, 1943.

25. Herrmann, H., and Friedenwald, J. S.: The Cholin Esterase Content of the Choroid Plexus and Ciliary Processes, Bull. Johns Hopkins Hosp. **70**:14, 1942.

26. Koelle, G., and Friedenwald, J.: A Histochemical Method for Localizing Cholinesterase Activity, Proc. Soc. Exper. Biol. & Med. **70**:617, 1949; The Histochemical Localization of Cholinesterase, Am. J. Ophth., to be published.

Retina and Optic Nerve.—Parasympathomimetic activity was demonstrated by Velhagen [19] in extracts of the retina of the rabbit, sheep and ox, and similar findings in the rabbit retina were reported by Bakker.[27] Nachmansohn [46] noted high esterase values for dog and ox retinas, while lower values were reported for the optic nerve of the ox by Brecht and Corsten.[28] The esterase activity of the optic nerve of the ox as measured by Weekers [29] was one-hundredth that of its retina; however, Loewi and Hellauer [30] found no cholinesterase whatever in the optic nerve. Cholinesterase activity was reported by Weve and Fischer [12] in the human retina and in the subretinal fluid obtained from patients with retinal detachment. In retinas of sheep embryos, as reported by Nachmansohn,[7b] enzyme activity increases as gestation progresses. Lindman [31] performed similar experiments on embryonic chick retinas and noted a sudden sharp rise in cholinesterase activity just prior to, and a drop after, hatching. This sudden sharp rise in enzyme activity occurs on the nineteenth day of gestation and corresponds to the appearance of the pupillary constrictor reflex, thus showing that function of the retinal neuronal units, as elicited by pupillary constriction, and enzyme activity are closely related. No difference in the cholinesterase content of the light-adapted or dark-adapted frog retina was noted by Therman.[32] Nakashima and Murata,[33] however, measured a greater quantity of such activity in the light-adapted frog retina, as well as in the rabbit retina, whereas Lange [34] observed higher enzyme levels in the dark-adapted frog retina.

Combining both histologic and chemical methods, Anfinsen [35] localized the highest cholinesterase activity in the synaptic layers of the bovine retina. Koelle and Friedenwald,[26] on the other hand, using a

27. Bakker, A.: Ueber Acetylcholinbildung in der Retina, Arch. f. Ophth. **141**:326, 1939.

28. Brecht, K., and Corsten, M.: Acetylcholin in sensiblen Nerven, Arch. f. d. ges. Physiol. **245**:160, 1942.

29. Weekers, R.: The Cholinesterase of the Retina, Acta ophth. **23**:161, 1945.

30. Loewi, O., and Hellauer, H., The Acetylcholine Content of the Nerves of Warm Blooded Animals, J. Physiol. **93**:34P, 1938.

31. Lindman, V.: The Cholinesterase and Acetylcholine Content of the Chick Retina, with Especial Reference to Functional Activity as Indicated by the Pupillary Constrictor Reflex, Am. J. Physiol. **148**:40, 1947.

32. Therman, P.: The Neurophysiology of the Retina, Acta Soc. Scient. Fenn. **2**:5-74, 1935.

33. Nakashima, M., and Murata, G.: Ueber die Cholinmenge der Hell- und Dunkelnetzhaut, Acta Soc. Ophth. jap. **43**:660, 1939, Zentralbl. f. d. ges. Ophth. **44**:539, 1940.

34. Lange, V.: Ueber das Vorkommen von Acetylcholin im hell- und dunkeladaptierten Auge, Ztschr. f. Physiol. Chem. **279**:73, 1943.

35. Anfinsen, C.: The Distribution of Cholinesterase in the Bovine Retina, J. Biol. Chem. **152**:267, 1944.

histochemical method, demonstrated the highest cholinesterase content in the bipolar cell layer of the retina. Chang and associates [36] observed that the acetylcholine content of the dog retina of the blindfolded eye was lower than that of the control eyes, apparently owing to prolonged functional disuse.

Miscellaneous Observations.—According to Glick and associates,[37] very low cholinesterase levels were measured in the lens of the pig, but very high values were reported in the lacrimal gland of the same animal. Rados [38] reported that the cholinesterase level of the blood in glaucomatous patients was within normal range. Working with sheep embryos, Nachmansohn [15] noted esterase activity in the extrinsic muscles of the eye.

Comment.—The reason for the contradictory and somewhat confusing results is manifold. In the first place, several investigators measured

TABLE I.—*Cholinesterase Activity of Tissues and Fluids of Normal Experimental Animal Eyes Expressed in Milligrams of Acetylcholine Hydrolyzed per Gram of Tissue or per Milliliter of Fluid in One Hour*

Author	Animal	Aqueous	Vitreous	Iris	Ciliary Body	Retina	Optic Nerve
Brückner [14]	Ox	0.08	4.0	32	16	95	...
	Calf	...	...	...	...	92	...
	Horse	0.12	0.2	...	...	79	...
Herrmann and Friedenwald [33]	Ox	...	...	...	4	...	...
	Pig	...	...	...	26	...	...
Nachmansohn [7]	Dog	...	...	...	...	134	16
	Ox	...	...	...	...	109	...
	Pigeon	...	...	...	...	...	13
	Sheep embryo	...	...	...	...	18-146	...

acetylcholine, i. e., the substrate, instead of the enzyme. Acetylcholine is an unstable substrate; it is hydrolyzed and reformed at a very rapid rate; thus it is meaningless to measure its concentration at any given time. The enzyme itself, cholinesterase, on the other hand, is comparatively stable, and its concentration in the tissues is relatively constant.

Furthermore, the early investigators knew little concerning the general properties of this enzyme, such as the stability, optimum p_H,

36. Chang, H.; Hsieh, W.; Lee, L., and Li, T.: Diminution of Acetylcholine Content of Retina After Prolonged Functional Disease, Proc. Soc. Exper. Biol. & Med. **43**:140, 1940.

37. Glick, D.; Lewin, A., and Antopol, W.: Occurrence of Choline Esterase in Swine, Proc. Soc. Exper. Biol. & Med. **40**:28, 1939.

38. Rados, A.: Blood Cholinesterase Values of Patients with Glaucoma, Arch. Ophth. **30**:371 (Sept.) 1943.

enzyme and substrate concentration and temperature range. Most of them used biologic methods of determination, which even now are not accurate; and many of them attempted to find the enzyme where one would not expect to find it, i. e., in the aqueous and vitreous. The enzyme is present in high concentrations in the tissues of the eye that contain muscle and/or nerve tissue, namely, the iris, ciliary body and retina.

Thus, when closely scrutinized, only a few of these papers stand up to present day criticism. In table 1 the values of the various authors who reported quantitative data on esterase activity in ocular tissues were recalculated and expressed in acetylcholinesterase (ACHE) units (mg. of acetylcholine hydrolyzed in one hour per gram of wet weight tissue or per milliliter of fluid at 37 C.) in an attempt to compare and correlate them with the results of this study.

C. METHODS

The earliest workers, Loewi,[1] Loewi and Navratil [2] and others, used biologic methods for determination of cholinesterase. The first chemical method, described by the Stedmans [3] in 1932, was based on titration of the acid formed with dilute sodium hydroxide. Ammon,[39] in 1933, described his manometric method, based on the Warburg technic, in which he measured the amount of carbon dioxide formed. The Stedman technic was modified by Vahlquist [40] in 1935; his method was based on continuous titration with sodium hydroxide solution at a fixed p_H, using a step photometer to observe the color reaction. In 1937 Abdon and Uvnäs [41] described yet another colorimetric technic, based on the reaction of ferric chloride with the acetic acid formed. Glick [42] invented a continuous electrometric titration procedure, employing a glass electrode, with such sensitivity that the hydrolysis of 1.81 mg. of acetylcholine could be measured.

Another micromethod, as shown by Linderström-Lang and Glick,[43] employed the Cartesian diver to measure minute amounts of esterase

39. Ammon, R.: Die fermentative Spaltung des Acetylcholins, Arch. f. d. ges. Physiol. **233**:486, 1934.

40. Vahlquist, B.: On the Esterase Activity of Human Blood Plasma, Skandinav. Arch. f. Physiol. **72**:133, 1935.

41. Abdon, N. O., and Uvnäs, B.: A Step-Photometric Method for Determining the Activity of Acetylcholin Esterase in Blood Plasma, Skandinav. Arch. f. Physiol. **76**:1, 1937.

42. Glick, D.: A Micro-Method for the Determination of Choline Esterase and the Activity—p_H Relationship of this Enzyme, Compt. rend. d. trav. du lab. Carlsberg, **21**:263, 1938.

43. Linderström-Lang, K., and Glick, D.: Micromethod for Determination of Choline Esterase Activity, Compt. rend. d. trav. du lab. Carlsberg, **22**:300, 1938.

activity. Histochemical procedures were described by Anfinsen and associates [44] and Koelle and Friedenwald.[46]

In the present study, I used the latest chemical method, developed by Hestrin,[45] and a more detailed description of it will be given later.

II. EXPERIMENTAL DATA

NORMAL ANIMALS

Since quantitative data concerning cholinesterase activity in the eye are somewhat confusing, and only fragmentary, it was decided to examine first the normal eyes of experimental animals.

Technic.—The animals were killed by bleeding or by an overdose of pentobarbital sodium (nembutal®) since a single lethal dose of this drug [46] does not affect the esterase activity. The eyes were enucleated, and the tissues were dissected, weighed and homogenized in the hand mortar, or in the Potter-Elvehjem tissue homogenizer, with a small amount of Berkshire sand and saline solution. The reaction mixture was then prepared by adding 1 part of saline homogenate to 2 parts of phosphate buffer (0.2 molar; p_H 7.3) and 1 part of acetylcholine chloride. The substrate concentration was 3.4×10^{-3} molar per milliliter of reaction mixture. This reaction mixture was incubated at 37 C. and continuously agitated on a revolving drum placed inside the incubator. At stated intervals aliquot parts were taken, and the amount of acetylcholine hydrolyzed was determined by Hestrin's [45] new colorimetric method. The aliquot removed from the reaction mixture was placed in a hydroxylamine-sodium hydroxide solution, which immediately stops the hydrolysis of the acetylcholine and converts it into hydroxamic acid. After this reaction has been allowed to continue for one minute, the p_H is lowered to 1.2 ± 0.2 with hydrochloric acid, and the color is brought out with a 10 per cent ferric chloride solution. Hestrin used the Klett spectrophotometer to record the color change, but in this study the Coleman spectrophotometer was employed, with the 540 millimicron wavelength. A standard curve was first prepared and plotted on logarithm paper; the result was a straight line from which the amount of acetylcholine hydrolyzed could be read off directly. Most of the readings were done at one-half, one and two hour intervals, and the rate of hydrolysis was calculated from the steepest slope of the activity-time curve. With proper dilutions the enzyme concentration was so adjusted that a linear rate of hydrolysis took place up to the one hour mark, after which the reaction rate slowly fell off. This linear reaction rate during the first hour was observed in most of the tissues examined. The sensitivity of this test is about the same as that of the conventional Warburg manometric method; i. e., the enzymatic hydrolysis of less than 50 micrograms of acetylcholine cannot be measured by either method.

44. Anfinsen, C.; Lowry, O., and Hastings, A.: The Application of the Freezing-Drying Technique to Retinal Histochemistry, J. Cell. & Comp. Physiol. **20**:231, 1942.

45. Hestrin, S.: The Reaction of Acetylcholine and Other Carboxylic Acid Derivatives with Hydroxylamine, and Its Analytical Application, J. Biol. Chem. **180**:249, 1949.

46. Schütz, F.: The Effect of Barbiturates on the Cholinesterase in Different Tissues, J. Physiol. **102**:269, 1943. Adriani, J., and Rovenstine, E.: The Effect of Anesthetic Drugs on Activity of Cholinesterase, Anesth. & Analg. **20**:109, 1941.

Most of the tissues examined were fresh, some having been kept in the refrigerator for twenty-four to forty-eight hours before use. As mentioned previously, cholinesterase is a relatively stable enzyme; this property of the enzyme was demonstrated in the present study by comparing freshly enucleated tissues with samples of the same tissue taken several days later. The comparison showed that if the dissected tissue or its saline homogenate was kept in the refrigerator the esterase activity remained unchanged for several days, sometimes as long as one week after enucleation.

Results.—Table 2 shows the results of the studies made on the normal eyes of experimental animals, all values being expressed in acetylcholinesterase (ACHE) units. Since in rabbits anatomic separation of the iris from the ciliary body is impossible,[47] these two tissues were examined as one; but to prevent confusion in the table the results are reported under both the iris and the ciliary body. The highest

TABLE 2.—*Cholinesterase Activity in Tissues and Fluids of Normal Experimental Animal Eyes Expressed in Milligrams of Acetylcholine Hydrolyzed per Gram of Tissue or per Milliliter of Fluid in One Hour*

Animal	Number of Eyes	Iris	Ciliary Body	Retina	Aqueous	Vitreous
Rabbit	50	98	98	130	0	0
Cat	15	55	227	160	0	..
Kitten	4	98	50	...	..	..
Dog	4	28	124	125	..	..
Pigeon	4	..	55	...	..	..
Rooster	4	115	72	183	..	..
Ox	10	44	24	...	0.56	5.6
Horse	10	20	10	...	0.16	0.2
Pig	6	56	45	...	..	..

activity—20 to 200 acetylcholinesterase units—was obtained in conductive tissues, i. e., tissues that contain nerves and/or muscles. The fluids of the eye, on the other hand, contained much less esterase, or none at all—0 to 5 acetylcholinesterase units. The retinas of the different animals examined showed approximately the same enzyme activity as that noted previously by Nachmansohn—130 to 183 acetylcholinesterase units (table 1). In the iris and ciliary body, however, the results varied considerably from species to species; e. g., enzyme activity in the ciliary body of the horse measured 10 acetylcholinesterase units, whereas the same organ of the cat showed a cholinesterase content of 227 acetylcholinesterase units.

47. Troncoso, M. U., and Castroviejo, R.: Micro-Anatomy of the Eye with the Slit-Lamp Microscope: The Comparative Anatomy of the Angle of the Anterior Chamber in Living and Sectioned Eyes of Mammalia, Am. J. Ophth. **19**:371, 1936. Davis, F. A.: The Anatomy and Histology of the Eye and Orbit of the Rabbit, Tr. Am. Ophth. Soc. **27**:401, 1929.

Histologic Study and Comment.—To find a plausible explanation for the variation in enzyme content of the ocular tissues in the different species of animals, an attempt was made to correlate the histologic picture with the enzyme activity. Histologic sections of normal cat, rabbit, pig and ox eyes were examined. It was observed that histologically the mammalian retina varied only a little from species to species, and, correspondingly, there was no drastic difference in the cholinesterase contents for the various species. In the iris and ciliary body, on the other hand, in which cholinesterase content varied considerably from species to species, the enzyme activity was related to the relative amount of muscle in these tissues. For example, it was observed that the ciliary body of the cat contained about ten times as much cholinesterase per gram of tissue as did that of the ox, and the microscopic section showed that in the cat most of the ciliary body consisted of ciliary muscle, there being very little connective tissue. Histologic sections of the ox eye showed just the opposite; here a relatively small ciliary muscle was surrounded by a great deal of connective tissue. The same correlation could be made between other animals, e. g., the rabbit and the pig. The ciliary muscle of the rabbit is small and poorly developed and has a relatively low esterase activity; the pig, on the other hand, had a good-sized ciliary muscle with a higher enzyme activity. Hence, the correlation for these animals could be expressed as follows: (1) poorly developed ciliary body and low cholinesterase activity (rabbit and ox); (2) large ciliary muscle and high enzyme activity (cat, dog and pig).

The iris followed a similar pattern. However, in addition to the correlation of the enzyme activity with the histologic picture, the degree of function of the iris could be correlated with its esterase activity. It was noted that the cat iris had twice the enzyme activity of the rabbit iris and that if light was projected into the eyes of these animals the rabbit pupil reacted slowly, sluggishly or sometimes not at all. The cat's pupil, however, had a very active light reflex, constricting maximally to a narrow slit, thus illustrating that the iris with the higher motor activity also has the higher enzyme activity. This observation demonstrated the functional significance of cholinesterase.

An interesting point was the very high value for the rooster iris; this observation can be explained by the fact that the iris constrictor in the rooster, as in most birds, is skeletal muscle, whereas in mammals it is smooth muscle. Armstrong [24] also noted high cholinesterase activity in the turtle iris, which has skeletal muscle, and low values for the amphibian iris, which has smooth muscle.

To explain varying enzyme concentrations in the different muscles, Nachmansohn [6] and associates examined histologic preparations of these muscles. These investigators used various staining methods to show the nerve end plates in the muscle, and they concluded that the

enzyme activity depended mainly on the amount of nerve tissue, i. e., the number of end plates, in relation to the amount and size of the muscle fibers. However, since the muscles in the iris and ciliary body are smooth muscles, and thus contain no end plates, Nachmansohn's method cannot be applied to these tissues. Another difficulty lies in the special character of the connective tissue of the iris and ciliary body. Stöhr,[48] who reviewed the subject in his textbook, stated that the connective tissue fibrils in the iris and ciliary body tend to take up the same stains as the nerve fibers. Therefore differential staining of the nerve fibers in the iris and ciliary body was not attempted.

In the light of present knowledge, it is impossible to find a reasonable explanation of the presence of the enzyme in the aqueous and vitreous. The fact is that in many animals it is present, but only in minute amounts. One might theorize and say that it finds its way into these fluids by diffusion from neighboring tissues that have a very high enzyme activity. It is possible that, during the process of cell degradation in the iris, ciliary body and retina, the broken-up cell particles, and with them cholinesterase, are carried into the aqueous and vitreous. Another possibility is that the enzyme present in the ocular fluids arises from the blood serum; in any case, it is difficult to see how the cholinesterase can have any functional significance in the aqueous and vitreous, where it is present only in minute amounts. Thus, contrary to the opinion of earlier workers, the importance of cholinesterase in the ocular fluids should be minimized.

The values observed in this study (table 2) are in fairly close agreement with those reported by Nachmansohn, but Brückner [18] and Herrmann and Friedenwald [25] obtained much lower results (table 1). The probable reason for their lower values is the excessive concentration of the substrate which was used by these authors. Nachmansohn and associates,[49] as well as Augustinsson,[5] demonstrated that the activity of the enzyme depends on the concentration of the substrate; when this activity is plotted against the concentration of the substrate, a typical bell-shaped curve is obtained, showing that too high a concentration of the substrate inhibits the esterase activity. The optimum concentration of the substrate is about 3 to 4×10^{-3} molar solution of acetylcholine. Brückner used a 1×10^{-2} molar solution, and Herrmann and Friedenwald, a 2.2×10^{-3} molar solution, both values being far above the optimum concentration.

Another reason for the low values obtained by the aforementioned authors might be found in their homogenation process; Brückner, for

48. Stöhr, P.: Mikroskopische Anatomie des vegetativen Nervensystems, Berlin, Julius Springer, 1928, pp. 212-214.

49. Nachmansohn, D.; Rothenberg, M., and Field, E.: Studies on Cholinesterase: V. Kinetics of the Enzyme Inhibition, J. Biol. Chem. **174**:247, 1948.

example, reported that after homogenizing the tissues in a glass mortar, by hand, he used only the supernatant fluid extract; thus, he unquestionably lost some of the enzyme in the small pieces of tissue remaining at the bottom of the mortar. In the present study the tissues were homogenized in ground glass tubes which were attached to a high speed electric motor, and it was observed that this process yielded much finer homogenates than those obtained by grinding the tissue by hand in the glass mortar. After running parallel experiments, I finally abandoned the manual grinding method, because the electric motor-driven process yielded higher and more consistent values.

Summary.—By means of a new chemical test, the cholinesterase activity was determined in the tissues and fluids of normal rabbit, cat, kitten, dog, pigeon, rooster, pig, ox and horse eyes.

1. The highest enzyme activity was measured in the muscle-containing and nerve-containing tissues, i. e., the iris, ciliary body and retina.

2. The aqueous and vitreous contained only traces of this enzyme.

3. The retinas of these animals showed approximately the same enzyme activity, but the irises and ciliary bodies varied considerably from one species to another.

4. The degree of cholinesterase activity in the iris and ciliary body of these different species was related to the amount of muscle present in these tissues.

Reasons are given for the differences between the values obtained in the present study and those reported in the literature.

SPECIFICITY OF THE ENZYME IN THE EYE

It is known that cholinesterase is not a single enzyme but that it denotes a whole group of enzymes. All these enzymes have the common property of splitting choline esters, but they are not necessarily specific for acetylcholine. Several attempts have been made to classify the cholinesterases and to divide them into certain well defined and recognizable categories. The Stedmans,[8] working with horse serum, were the first to discuss the types of cholinesterase. In the last few years Nachmansohn, with Rothenberg [50] and with Augustinsson,[51] using several methods of approach to this question, classified the cholinesterases as follows:

Group 1.—First, there are the "specific," "true" or "pure" cholinesterases, called "acetylcholinesterase" by Nachmansohn and Augustins-

50. Nachmansohn, D., and Rothenberg, M.: On the Specificity of Choline Esterase in Nervous Tissue, Science **100**:454, 1944.

51. Augustinsson, K. M.: Substrate Concentration and Specificity of Choline Ester-Splitting Enzymes, Arch. Biochem. **23**:111, 1949. Augustinsson, K. M., and Nachmansohn, D.: Distinction Between Acetylcholine-Esterase and Other Choline Ester-Splitting Enzymes, Science **110**:98, 1949; Studies on Cholinesterase: VI. Kinetics of the Inhibition of Acetylcholine Esterase, J. Biol. Chem. **179**:543, 1949.

son, their specific ester being acetylcholine. They have a low Michaelis constant, which means that their affinity to acetylcholine is high, and their optimum activity is at about a 3×10^{-3} molar solution of acetylcholine. Propionylcholine is split at about the same, or at a slightly lower, rate, and butyrylcholine, at a much lower rate; but all the other esters are hydrolyzed at a very low rate or not at all. If the cholinesterase activity is plotted against the acetylcholine concentration, a bell-shaped curve is produced, showing that the enzyme is inhibited by an excess of its substrate. This is a typical reaction, manifested by many other enzymes. These specific cholinesterases occur mainly in conductive tissues, i. e., muscle and nerve tissue, as well as in red blood cells.

GROUP 2.—Next there are the "nonspecific" cholinesterases, or "pseudocholinesterases." Both propionylcholine and butyrylcholine are split by these enzymes at a much higher rate than is acetylcholine, and they have a low affinity for acetylcholine; i. e., the Michaelis constant is high. Their behavior is consistent with the Michaelis-Menten theory; that is they are not inhibited by high acetylcholine concentrations. On the contrary, these cholinesterases show optimum activity only at an excess concentration of substrate. They occur characteristically in the serums of man and of certain animals, as well as in the pancreas.

Two methods are available for classification of a cholinesterase. The first consists in the use of several choline esters at a fixed concentration; the other, in using different concentrations of the substrate, since it is known that the activity–substrate concentration relation differs for any given enzyme from one substrate to another.

Nachmansohn, with Rothenberg [50] and Augustinsson,[51] tried both methods with a great variety of tissues and with several purified enzymes. Since both these methods obtained substantially the same results, it was decided to use only the first procedure in this study. In this paper the enzyme characteristic of group 1 will be called specific cholinesterase and the enzyme characteristic of group 2 will be referred to as nonspecific cholinesterase.

One must bear in mind that this classification of the cholinesterases into specific and nonspecific types is only relative, and not absolute. The chances are that in any given tissue there are several cholinesterases, but usually those of one or the other type predominate. Since at present separation of the different esterases is impossible, one must be satisfied with this scheme of classification; the arrangement is not ideal, but it is certainly better than no classification at all.

Method.—Three choline esters, acetylcholine, propionylcholine and butyrylcholine were used at 3.4×10^{-3} molar concentration, and the cholinesterase activity of the various tissues was determined, as described in part I.

Great care must be exercised with propionylcholine and butyrylcholine, because these compounds are even more unstable than acetylcholine. Substrate controls must be run with each experiment to test for spontaneous hydrolysis, and, should this occur, allowance for it must be made in the final calculations.

The amount of acetylcholine hydrolyzed is taken as 100, and the values obtained for propionylcholine and butyrylcholine are expressed as percentages thereof.

Results.—Charts 1 to 6 demonstrate that the muscle-containing and nerve-containing tissues of the eye, i. e., the iris and the ciliary body, contained the specific cholinesterase; if the rate of hydrolysis for acetylcholine was taken as 100, approximate values for propionylcholine and butyrylcholine were 75 and 35 per cent, respectively, the only exception

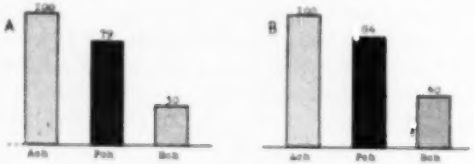

Chart 1.—Pattern of cholinesterase activity in the serum (*A*) (6 samples) and the iris and ciliary body (*B*) (6 eyes) of the rabbit in the presence of acetylcholine (*Ach*), propionylcholine (*Pch*) and butyrylcholine (*Bch*). The columns represent activity rates in percentages, the value for acetylcholine being 100.

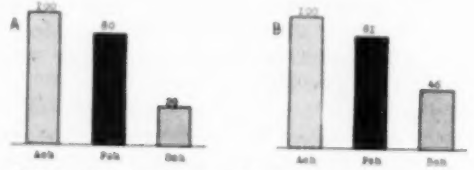

Chart 2.—Pattern of cholinesterase activity in the ox iris (*A*) and ciliary body (*B*) in the presence of acetylcholine (*Ach*), propionylcholine (*Pch*) and butyrylcholine (*Bch*) (6 eyes). The columns represent activity rates in percentages, the value for acetylcholine being 100.

being in the ciliary body of the horse, in which the values for these choline esters were higher than that for acetylcholine. The specific cholinesterase was noted in the rabbit serum and in the aqueous and vitreous of the ox.

The nonspecific type of cholinesterase was observed in the serum and the secondary aqueous of the cat. Primary aqueous, removed from 12 cat eyes under pentobarbital anesthesia, showed no esterase activity with any of the esters used. After twenty minutes the secondary aqueous was withdrawn, and it showed a hydrolysis pattern similar to that of the serum, i. e., typical of the nonspecific esterase. In these fluids

hydrolysis rates for propionylcholine and butyrylcholine were approximately 140 and 250 per cent, respectively.

Two retinas each from dog, cat, rabbit, ox and horse eyes were tested with the three substrates; as one would expect with nerve tissue, they all showed the pattern typical of the specific cholinesterase. Experiments for esterase specificity were carried out also on the aqueous and vitreous of the horse, but, because the values obtained were very low and erratic, and thus unreliable, they were not included in this report.

Comment.—On purely theoretic grounds, one would expect to find the specific cholinesterase in the muscle-containing and nerve-containing tissues of the eye—and indeed this was the case, as shown by experimental evidence. However, a few notable exceptions were observed.

Chart 3 demonstrates that the aqueous and vitreous of the ox contained the specific type of cholinesterase. This leads to interesting speculations; one might say that the esterase in these ocular fluids must come from the iris and ciliary body, since it is specific; one could go even further and say that it cannot come from the serum because in

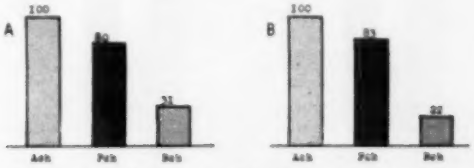

Chart 3.—Pattern of cholinesterase activity in the ox aqueous (*A*) and vitreous (*B*) in the presence of acetylcholine (*Ach*), propionylcholine (*Pch*) and butyrylcholine (*Bch*) (20 eyes). The columns represent activity rates in percentages, the value for acetylcholine being 100.

that case it would be nonspecific. Unfortunately, the last statement cannot be substantiated by experimental evidence. Ox serum, when tested for esterase activity with acetylcholine, propionylcholine and butyrylcholine, gave very low values, or none at all, for all three esters. On the other hand, since the serum presents only a trace of esterase activity and the ocular fluids show measurable amounts, it is reasonable to assume that the esterase in the ocular fluids could not have come from the serum. Hence, one arrives at the conclusion that the cholinesterase in the ocular fluids of the ox comes from the iris and ciliary body, probably by diffusion.

Chart 4 shows that in the iris of the horse the specific type of cholinesterase predominated, but the ciliary body of this animal presented a pattern typical of nonspecific cholinesterase. The explanation of this interesting observation may be explained as follows: The ciliary body of the horse contains only a small, poorly developed ciliary muscle,

and consequently only a small amount of specific cholinesterase. The ciliary body, being a highly vascular structure, contains a relatively large amount of serum; and since horse serum shows high esterase activity of the nonspecific type, one can assume that the highly active nonspecific cholinesterase in the serum overshadows the relatively small amount of specific cholinesterase in the ciliary muscle. Therefore, the ciliary body taken as a whole will show only the nonspecific type of

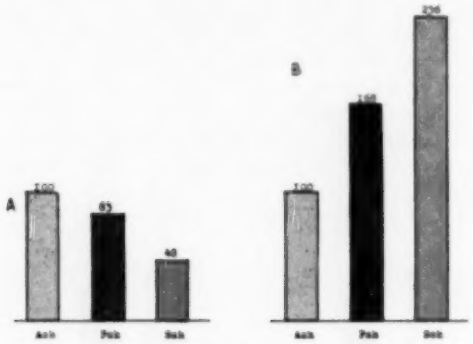

Chart 4.—Pattern of cholinesterase activity in the horse iris (*A*) and ciliary body (*B*) in the presence of acetylcholine (*Ach*), propionylcholine (*Pch*) and butyrylcholine (*Bch*) (5 eyes). The columns represent activity rates in percentages, the value for acetylcholine being 100.

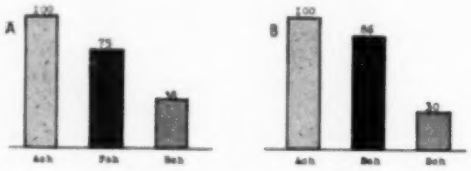

Chart 5.—Pattern of cholinesterase activity in the cat iris (*A*) and ciliary body (*B*) in the presence of acetylcholine (*Ach*), propionylcholine (*Pch*) and butyrylcholine (*Bch*) (6 eyes). The columns represent activity rates in percentages, the value for acetylcholine being 100.

esterase. This is a good illustration of the fact that if there is a mixture of various cholinesterases only the predominating type will manifest itself with this method of differentiation.

Another interesting fact to be noted was the presence of nonspecific cholinesterase in the serum and the secondary aqueous of the cat. Jaffe [18] reported that the secondary aqueous of the cat has measurable cholin-

esterase activity and that this cholinesterase probably comes from the serum. This assumption has now been definitely confirmed by the experiments reported here, and it seems entirely logical in the light of what is known of the other characteristics of the secondary aqueous.

Summary.—The specificity of cholinesterase is discussed.

It was shown that the iris, ciliary body and serum of the rabbit; the iris, ciliary body, aqueous and vitreous of the ox; the iris of the horse; the iris and ciliary body of the cat, and the retina of the dog, cat, rabbit, ox and horse, all demonstrated a hydrolysis pattern typical of that of the specific cholinesterase.

The nonspecific cholinesterase was observed in the ciliary body of the horse and in the serum and the secondary aqueous of the cat.

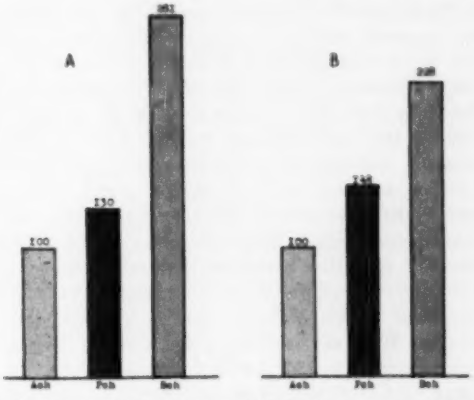

Chart 6.—Pattern of cholinesterase activity in the cat serum (*A*) (6 samples) and secondary aqueous (*B*) (12 eyes) in the presence of acetylcholine (*Ach*), propionylcholine (*Pch*) and butyrylcholine (*Bch.*) The columns represent activity rates in percentages, the value for acetylcholine being 100.

It was proved that in the secondary aqueous of the cat the cholinesterase is derived from the serum.

It is assumed that in the ox eye cholinesterase found its way into the aqueous and vitreous from the iris, ciliary body and retina.

STUDIES ON HUMAN SUBJECTS

Ever since the discovery of cholinesterase, many attempts have been made to relate this enzyme to the problem of glaucoma. The main reason for this interest was due to the well known therapeutic effect of the inhibitors of cholinesterase in several types of glaucoma. Even

before physostigmine was known to be an inhibitor of cholinesterase, it was widely used in glaucomatous conditions, and lately diisopropyl fluorophosphate (DFP), another well known inhibitor of cholinesterase, has been added to the antiglaucomatous agents.

Since the etiology of chronic simple glaucoma is unknown, several investigators tried to link this ocular disease with cholinesterase activity. Most of them studied the aqueous, obtained from the eyes of patients, both normal and glaucomatous; but, as mentioned in part 1, their results were contradictory. Some found cholinesterase activity in the aqueous of normal subjects, and others did not; some observed increased esterase activity in the aqueous of glaucomatous eyes, whereas others noted lessened activity.

The main reason for this confusing picture was their use of the intraocular fluids, instead of the nerve-containing and muscle-containing tissues, for enzymatic determinations. The enzymatic hydrolysis of acetylcholine by cholinesterase is an intracellular or a cell surface phenomenon. It occurs on or near the neuronal surface, i. e., along the length of the nerve fiber, at the synapses and at the myoneural junction. Therefore, in the eye one should expect to find this enzyme mainly in the nerve-bearing and muscle-bearing tissues, i. e., in the iris, ciliary body and retina, and, as shown in part 1 of this report, this was demonstrated in the experimental animal. It is highly probable that a water-soluble enzyme, such as cholinesterase, can find its way into the aqueous from the neighboring tissues or from the blood serum. But it is unwarranted to assume that this minimal amount of cholinesterase—occasionally found in the aqueous—has an essential function. Yet previous workers have not only assumed such an essential function, but have even attempted to link it with the cause of glaucoma. It would seem, therefore, that if cholinesterase has anything to do with glaucoma one should examine the tissues involved in this disease which do contain the enzyme, viz., the iris and the ciliary body. It was with this thought in mind that the following study was undertaken.

Technic.—The human eyes were obtained from the operating room of the Institute of Ophthalmology and from the Eye Bank for Sight Restoration, Inc. The normal tissues were obtained from globes the corneas of which were used for corneal transplantation. All reached the laboratory within forty-eight hours after enucleation, and, since they were kept in the refrigerator during this period, for esterase determinations they were normal and fresh. The glaucomatous and degenerated eyes were obtained fresh from the operating room through the courtesy of the surgeons of the Institute of Ophthalmology, and the specimens of the extraocular muscles came from 8 consecutive recession-resection operations for the correction of strabismus. The records of the patients were carefully examined to eliminate from this series those who had received anticholinesterase drugs prior to enucleation. The eyes were dissected, and cholinesterase activity was determined in the usual manner.

Results.—Table 3 shows the cholinesterase activity in the tissues of the normal human eye. The iris contained about the same values as that of most of the experimental animals studied—30 acetylcholinesterase units—but the ciliary body showed exceptionally high enzyme activity—355 acetylcholinesterase units—the values being higher than those shown in any of the experimental animals. The extraocular muscles, which were included with the normal tissues, showed in comparison with other skeletal muscles an exceptionally high cholinesterase content—44 acetylcholinesterase units.

TABLE 3.—*Cholinesterase Activity of Tissues of the Normal Human Eye, Expressed in Milligrams of Acetylcholine Hydrolyzed per Gram of Tissue per Hour*

	Extraocular Muscle	Iris	Ciliary Body
	50	15	397
	45	41	...
	45	39	407
	54	45	...
	38	26	...
	44	39	...
	34	23	304
	43	29	...
	..	33	270
	..	26	360
	—	—	—
Average	44	30	355

TABLE 4.—*Cholinesterase Activity of Tissues of Pathologic Human Eyes Expressed in Milligrams of Acetylcholine Hydrolyzed per Gram of Tissue per Hour*

Absolute Glaucoma		Degenerated Globe	
Ciliary Body	Iris	Ciliary Body	Iris
...	4	...	0
...	12	...	0
258	0	129	8
240	8	225	20
288	42	275	44
—	—	—	—
Average 266	13	242	11

Table 4 demonstrates the enzyme activity in the tissues of diseased human eyes, the average values being 12 and 270 acetylcholinesterase units for the iris and ciliary body, respectively.

Comment.—In accordance with the line of reasoning outlined in part 1, the chemical data were again related to the histologic picture. Histologic preparations of normal human eyes showed that while in the iris the muscle formed only a small part of the total tissue, in the ciliary body the situation was reversed; here one could observe a large, well developed muscle and only a small amount of connective tissue stroma around it. Thus it could be observed that the tissue with only a small amount of muscle—the iris—had a low cholinesterase content; on the

other hand, the tissue with a large amount of muscle—the ciliary body—showed a high enzyme activity. Since the ciliary body contains the muscle of accommodation, it is only appropriate that in Homo sapiens this structure should be better developed than in the rest of the animal kingdom. Its cholinesterase activity seems to bear out this assumption.

The reason for the high cholinesterase content observed in the extraocular muscles is a relatively greater number of nerve end plates in these muscles, which accounts for a relatively greater proportion of nerve tissue per unit weight of muscle, causing an increased cholinesterase activity. Nachmansohn,[7b] who studied the extraocular muscles of sheep embryos, reported similar results. It is well known that the extraocular muscles, as compared with other skeletal muscles, have a high motor activity; hence this example well illustrates that the higher the motor activity of an organ, the greater its cholinesterase content.

Table 4 presents the cholinesterase activity in the tissues of the pathologic human eye. The patients had absolute glaucoma or had degenerated, atrophic globes of many years' standing, and the results show that the irises and ciliary bodies of these eyes had a lower cholinesterase activity than was noticed in the tissues of the normal eyes. However, there was little, if any, difference in cholinesterase activity between the absolute glaucomatous eyes and the degenerated globes. Thus, in the light of the evidence presented, it can be stated that at the end of a long drawn-out disease, such as absolute glaucoma, or in degenerated, atrophic eyes, the cholinesterase content of the iris and ciliary body is decreased; but this certainly is not sufficient evidence to justify the linking of cholinesterase activity with the problem of glaucoma.

The next logical step would be to study the enzyme activity of the iris in chronic simple glaucoma, i. e., at the earliest possible start of the disease, instead of in its final phase. Such a study, however, would encounter several serious difficulties. To begin with, since eyes with chronic simple glaucoma are not enucleated, one could not obtain a whole iris, and the small parts of irises which are removed during the course of various operations for glaucoma weigh only 2 to 4 mg., whereas the chemical method which I use requires at least 10 mg. of iris for accurate enzyme studies. One could attempt to use micromethods, but this still leaves the difficulty of measuring wet weights; if the total amount of tissue is 2 to 4 mg., the error in weighing may be anywhere from 50 to 100 per cent. Another factor to be considered is the state of contraction of the iris, which will vary considerably with each individual eye. If the whole iris is removed, this disadvantage is eliminated; but if only a small trephine button or a piece obtained from an iridectomy is used, one can never be certain how much of the tissue

removed is muscle and how much is connective tissue. Because of these difficulties, determinations of cholinesterase activity in the irises of patients with chronic simple glaucoma were not attempted.

Summary.—Human extraocular muscles show a high cholinesterase activity.

The iris and ciliary body of eyes with absolute glaucoma and degenerated atrophic globes contain less cholinesterase than do the corresponding structures of normal eyes.

Experimental evidence has failed to show a causal relation between cholinesterase activity and the problem of glaucoma.

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The propionylcholine and the butyrylcholine were obtained through the courtesy of Dr. J. A. Aeschlimann, of Hoffmann-LaRoche, Inc., Nutley, N. J. Some of the human tissues were received from the Eye Bank for Sight Restoration, Inc., through the cooperation of Mrs. Augusta Breckenridge.

OSMOTIC PRESSURE OF THE EXTRAOCULAR AND INTRAOCULAR FLUIDS

A. J. SCHAEFFER, M.D.
LOS ANGELES

THE AVAILABLE data concerning molar concentration of the ocular fluids, though of great theoretic and practical interest to the physician, the physiologist and the pharmacologist, are in a very confused state. Final clarification of the problems involved is desirable, since on such data theories of origin of the intraocular fluid and water movements in the eye and its tissues are constructed; furthermore, the increasing interest in the production of isotonic fluids used for therapeutic purposes indicates the practical importance of these problems.

THE TEARS

According to the generally accepted concept, the tears are isosmotic with a 1.4 per cent sodium chloride solution, and the recommendation for adjusting the osmotic concentration of collyriums to this presumed tonicity has found worldwide acceptance. "Pharmacopoea Helvetica," 1933; "Pharmacopoea Gallica," 1937; "Dispensarium Danicum," 1934-1938, and "Pharmacopoea Svecica," 1943, all state that solutions for instillation into the eye should be isotonic with a 1.4 per cent sodium chloride solution, which, by implication, corresponds to the osmotic concentration of tears.

The question of the physicochemical constitution of solutions for ophthalmic use, involving such factors as osmotic pressure and p_H, with regard to permeability, therapeutic effectiveness, preservation and, last but not least, comfort in use, I have already discussed.[1] Such problems are completely ignored in ophthalmic formularies of recent date, such as those of Lewis[2] and Harrison.[3]

1. Schaeffer, A. J.: Some Aspects of Ophthalmo-Pharmacology: I. Fundamental Principles, Docum. ophth., to be published.

2. Lewis, G. G.: The Ophthalmic Formulary, Springfield, Ill., Charles C Thomas, Publisher, 1942.

3. Harrison, W. J.: Ocular Therapeutics, Springfield, Ill., Charles C Thomas, Publisher, 1947.

Recommendations for adjustment of collyriums, on the other hand, are to be found in the recent papers of Mellen and Seltzer and others [4] which present a list of drugs and their concentrations isotonic with 1.4 per cent sodium chloride solution in water. Since most such solutions are used in heterotonic concentrations, an adjustment to the hypothetic isotonicity is necessary. Of course, when the therapeutic concentration of the drug should be hypertonic to a 1.4 per cent sodium chloride solution, there is no way of effecting an adjustment except by lowering the therapeutic concentration. On the other hand, since most of these drugs in the required concentration are hypotonic, it is recommended that various amounts of sodium chloride be added to render the solution isotonic. To facilitate the calculation of the tonicity adjustment, a table of tonic equivalents has been given by Mellen and Seltzer,[4a] from which the amount of sodium chloride needed can be calculated. Such systems of adjustment were accepted and recommended by ophthalmologists, for example, Elvin [5] and Grosz.[6] The same recommendation has been given by pharmacologists, among them Arrigoni and Tozer [4c] and Goyan and associates.[7] Calculations for the addition of sodium chloride to render a collyrium "isotonic" are usually based on the formula of Nicola. The osmotic pressure in any solution is directly proportional to the concentration, the degree of dissociation and the molecular weights of the dissolved substances. The concentration is expressed as the percentage weight divided by the volume of the solute. The degree of dissociation is determined by the approximate dissociation constants.

Such calculations are therefore somewhat complicated by the fact that electrolytes and nonelectrolytes behave differently in solution. In a solution of electrolytes, the electrolytic dissociation, i. e., the ionic activity of the electrolytes, must be taken into consideration; and it can be determined by the approximate dissociation constants. A sodium chloride solution, for example, has a 1.8 times as great an osmotic activity as an equimolar solution of a nonelectrolyte. Tables like those of Mellen and Seltzer and of Elvin greatly facilitate the calculation.

4. (*a*) Mellen, N., and Seltzer, L. A.: Isotonic Buffer Solutions, J. Am. Pharm. A. **25**:759, 1936. (*b*) Arrigoni, L., and Fischer, L.: The Relation of p_H and Osmotic Pressure to Ophthalmic Solutions, Am. J. Pharm. **115**:23, 1943. (*c*) Arrigoni, L., and Tozer, G. A.: Ophthalmic Solutions, J. Am. Pharm. A. (Pract. Ed.) **7**:292, 1946.

5. Elvin, N. C.: The p_H and Tonicity of Ophthalmic Solutions, Arch. Ophth. **29**:273 (Feb.) 1943.

6. Grosz, I.: Ueber die Standardisierung der Augentropfen, Acta ophth. **22**: 147, 1944.

7. Goyan, F. M.; Enright, J. M., and Wells, J. M.: Critical Graphical Methods for Calculating Isotonic Concentrations and Freezing Points of Aqueous Solutions, J. Am. Pharm. A. (Scient. Ed.) **33**:74, 1944.

Similar principles were followed by Grosz.[8] He reported that a Hungarian pharmacologist, Doczy, constructed a slide rule to facilitate the calculation of the amount of sodium chloride necessary to add to therapeutic solutions in adjusting their molar concentrations isosmotically with a 1.4 per cent sodium chloride solution. In his calculation, the lowering of the freezing point of the active substance in solution and the lowering of the freezing point of the sodium chloride are the known factors.

When the available data on the osmotic concentration of the lacrimal fluid are analyzed, one comes to the conclusion that the a priori acceptance of the concept that tears are isosmotic with a 1.4 per cent sodium chloride solution is hardly tenable.

Among the newer data, the measurements of the osmotic concentration of tears by Ridley [8] are to be mentioned, though they have not found much consideration in the ophthalmologic literature. This author determined the osmotic pressure of tears of 3 persons by lowering the freezing point, using a Beckman thermometer. In all cases the osmotic pressure of tears was found to be slightly below that of the blood, and he concluded that tears might be considered, at least with regard to the diffusible components, as a dialysate from the blood. He found that tears and aqueous are similar in constitution and in osmotic concentration and that it is very likely that both are produced by similar processes from the blood.

The most exact measurement of the osmotic concentration of the lacrimal fluid was done by Krogh and associates,[9] and this work led to a different conclusion. They used Hill's very accurate vapor pressure method with Krogh's modification. Five men and 5 women were donors. These investigators found that the osmotic concentration of the samples examined corresponded to that of sodium chloride solutions of 0.87 to 0.92 per cent, the average being 0.9 per cent sodium chloride. For the same subjects the average osmotic concentration of the serum corresponded to a 0.86 per cent sodium chloride solution. Even this difference might have been artificial, as slight concentration by evaporation was inevitable.

These investigators also repeated Massart's experiment, to determine the limits of tolerance to changes in osmotic pressure by instilling saline solutions of various concentrations into the conjunctival sac. They

8. Ridley, F.: The Intra-Ocular Pressure and Drainage of Aqueous Humor, Brit. J. Exper. Path. **11**:217, 1930; An Experimental Investigation into the Intra-Ocular Pressure and Drainage of the Aqueous Humor, Tr. Ophth. Soc. U. Kingdom **50**:268, 1930.

9. Krogh, A.; Lund, C. G., and Pedersen-Bjergaard, K.: The Osmotic Concentration of Human Lacrymal Fluid, Acta physiol. Scandinav. **10**:88, 1945.

found that concentrations varying from 0.6 to 1.3 per cent were well tolerated, and only divergencies from "physiologic salt solution" greater than these were perceived as disagreeable, an observation suggesting that the adjustment of collyriums should not follow the concentration of the generally accepted 1.4 per cent sodium chloride solution but, rather, should correspond to the "physiologic" 0.9 per cent solution.

In a series of experiments, I attempted to influence corneal regeneration by local application of an amino acid–containing solution and found that such applications may accelerate considerably the rate of regeneration and that the effect of this acceleration is mainly due to the presence of cystine in the solution.[10] The osmotic pressures of these amino acid solutions were adjusted closely to a 0.9 per cent sodium chloride solution. These results are in contradiction to those of Gundersen and Liebman,[11] who determined the inhibitory effect of local anesthetics on the epithelial regeneration. These authors came to the conclusion that the regeneration is modified in degree also by the tonicity of the applied solutions and found that higher osmotic pressures favored regeneration. In my experiments, the osmotic activity of the amino acid solutions, equal to the tonicity of a sodium chloride solution of 0.9 per cent or slightly higher, did not influence the rate of epithelization in any way. Concentrations lower or higher than these values began to inhibit the healing process, and this inhibition was definite at concentrations lower than 0.8 per cent or higher than 1.3 per cent. In sensitivity tests, instillations of varying concentrations of sodium chloride solutions on myself and on other subjects led to results similar to those of Krogh and associates.[9]

I have arrived at similar conclusions in experiments on the fluid of contact lenses.[1] Stimulated by personal communications with Obrig, I have tried to apply the amino acid solution used for stimulation of epithelial wounds as a contact fluid. The stock solution contained 2 mg. of cystine, 5 mg. of proline, 6 mg. of asparagine and 14 mg. of glutamine per milliliter and was adjusted to a p_H of 7.2. The solution contained also a preservative, a combination of the two parahydroxybenzoic acid esters methyl paraben U. S. P. (nipagin M®) and propyl parahydroxybenzoate (nipasol®). The stock solution could be adjusted to a desired osmotic concentration. When this concentration was equivalent

10. Schaeffer, A. J.: Effect of Certain Amino Acids on Healing of Experimental Wounds of the Cornea, Proc. Soc. Exper. Biol. & Med. **61**:165, 1946; cited in Amino Acid Acceleration of Wound Healing, editorial, J. A. M. A. **131**: 1061 (July 27) 1946; An Attempt to Influence Corneal Wound Healing by Local Application of Certain Amino Acids, Am. J. Ophth., to be published.

11. Gundersen, T., and Liebman, S. D.: Effect of Local Anesthetics on Regeneration of Corneal Epithelium, Arch. Ophth. **31**:29 (Jan.) 1944.

to a 0.9 per cent sodium chloride solution, its tolerability was highest. At an osmotic concentration equivalent to a 1.4 per cent sodium chloride solution, it could not be tolerated, often not even for a matter of minutes, a finding in harmony with the rest of our observations.

Considering the discrepancies between the results of the two groups of investigators, namely, Krogh and associates and myself, on the one hand, and all the other authors, on the other, reexamination of the problem by measuring the molar concentration of tears on a larger scale seemed advisable.

TECHNIC

In these experiments, I attempted to reduce the margin of error due to rapid evaporation of water from the lacrimal fluid. The eye was fitted with a curved, transparent, air-tight plastic cover, through a small hole in which the capillary tube for obtaining the lacrimal fluid to be examined was introduced; the opening was sealed with petrolatum U. S. P. The fluid was taken up into the tube by capillarity from the inner side of the lower conjunctival sac, the first tubes being discarded. The sampling tubes were immediately sealed at one end.

The estimation of the osmotic pressure of small amounts of fluid does not lend itself to "direct" measurement. The same can be said of the method of plasmolysis. An estimation founded on calculation of the active constituents in solution by means of an equation is also not admissible in the case of a complex solution, such as the lacrimal fluid. On the other hand, two other methods, the lowering of the freezing point, as applied by Ridley, and the vapor pressure method, used in the studies of Krogh and associates, lend themselves, especially the latter, to such investigations. The method used in my study was based on the same principle. I followed the technic recommended by Niederl and Levy,[12] which is a modification of Barger's widely used method. This procedure has the great advantage of being simple and very sensitive and does not require complex instrumentation. It consists in the use of a closed system in which two fluids contained in capillary tubes are confronted: one, a given standard solution of known molarity, and the other, a solution of unknown molarity. Changes in volume of the fluids within the closed system after a period of time—four or more days—are indicative of differences in osmotic pressure. The two capillary tubes are filled with the respective fluids, sealed at one end and confronted in such a way that the fluid margins at the open ends of the capillary tubes are exactly at the same level. For convenience, this level can be marked, and the exactness of the position and marking may be controlled by low magnification under a microscope. The two capillary tubes so confronted are placed in a narrow external glass tube and evacuated to about 15 mm. of pressure, and the external tube is then sealed over a Bunsen flame. This closed system is kept at constant room temperature, and after four or more days the position of the meniscuses, i. e., the upper margins of the two fluids, is examined: If the two meniscuses are at the same level, the fluids have identical osmotic pressures; if they are changed, and the two meniscuses are not at the same level, the two fluids are hetero-osmotic. The distance between the two levels can be measured with a micrometer scale. The solution which has lost less

12. Niederl, J. B., and Levy, A. M.: Molecular Weight by Isothermic Distillation, Science **92**:2384, 1940.

solvent is the solution with the higher molarity. According to the authors, differences of ± 0.01 mole (approximately equivalent to 0.06 Gm. of sodium chloride per hundred cubic centimeters) can be measured in this way. It seems to me that the method has a somewhat higher sensitivity for physiologic fluids and that more delicate changes can be estimated further by microscopic examination of the induced differences. Such an improvement of the method is being attempted, and the results will be published later.[12a]

In preliminary measurements, in which the actual values were approximated, the method was simplified in that for every sample of tears one or more samples of sodium chloride solution were confronted with standards of 0.83 to 0.95 per cent sodium chloride solution. The relative gain or loss in solvent of each sample pair, as compared with the standard solution, indicated that molarity values as small as fractions of the isotonicity of a 0.05 per cent solution of sodium chloride

TABLE 1.—*Osmotic Activity of Tears, Expressed in Millimoles of Sodium Chloride per Kilogram of Water*

Men	Women	Children
160 —	160 —	150 +
160 +	160 —	160 —
170 —	160 —	—+—
170 +	160 +	Average 159 +
150 +	160 —	
150 +	160 +	
160 —	——	
160 —	Average 160 ±	
150 +		
160 —		
160 —		
160 —		
——		
Average 160 ±		

Total average, 160 ± mM sodium chloride per kilogram of water.

could be determined. This method made complex calculations unnecessary and gave values already compared and expressed in terms of isotonicity with sodium chloride solutions. Table 1 presents the findings for the 20 patients examined.

RESULTS

The osmotic concentration of the lacrimal fluid was estimated for 20 patients, and the results were arranged in table 1 according to sex and age. The molar concentrations showed a variation of 150+ to 170+ millimoles of sodium chloride, the average being 160± millimoles. This result coincides fairly well with the findings of Krogh and associates. The difference might be explained by the caution observed in the present study in excluding the possibility of evaporation from the surfaces of

12a. An instrument suitable for determining the osmotic pressure of biologic solutions, which uses the principles of Niederl and Levy, has been built and may be procured from Mr. V. L. Frykman at the Precision Instrument Shop of the University of Southern California in Los Angeles.

the eye by application of an air-tight shield over the eye under investigation. My results suggest that young persons produce tears with lower osmotic activity, as shown by the 2 adolescents. Of course, such a conclusion would be admissible only on the basis of a larger number of persons studied. No definite difference was seen in the osmotic concentration of the lacrimal fluid of men and of women.

These findings may be summarized by stating that the assumed osmotic concentration of the lacrimal fluid, 1.4 per cent sodium chloride, has no experimental confirmation. The present investigation confirms the findings of Krogh and associates [9] that the lacrimal fluid is isosmotic with a 0.9 per cent sodium chloride solution with only minor variability. The collyriums, according to these findings, should be adjusted to isotonicity with a 0.9 per cent solution of sodium chloride.

TABLE 2.—*Osmotic Activity of Aqueous Humor and Blood Serum of Man*

	Osmotic Activity, Millimoles Sodium Chloride per Kilogram of Water	
Case No.	Blood Serum	Aqueous Humor
1	160 —	160 —
2	160 —	160 +
3	160 +	160 +
4	160 —	160 —
Average 160 ±		

Aqueous Humor.—There is more satisfactory information on the osmotic activity of the aqueous humor than on that of the tears. This is understandable, since the molar concentration of the aqueous humor had to be investigated in relation to problems of origin, movements and elimination of the intraocular fluid.

In a recent investigation, Benham, Davson and Duke-Elder,[13] using Baldes' modification of the thermoelectric method, showed that the molar concentration of the aqueous humor of the dog and cat is higher than that of the corresponding serum by an amount averaging 0.0004 molar sodium chloride solution. The findings of a higher osmotic pressure of the aqueous humor was also confirmed in the investigations of Roepke and Hetherington [14] and Bárány.[15] General anesthesia raises the molar

13. Benham, G. H.; Davson, H., and Duke-Elder, W. S.: The Total Osmotic Concentrations in Serum and Aqueous Humour, J. Physiol. **89**:61, 1937.

14. Roepke, R. R., and Hetherington, W. A.: Osmotic Relations Between Aqueous Humor and Blood Plasma, Am. J. Physiol. **130**:340, 1940.

15. Bárány, E. H.: The Relative Importance of Ultrafiltration and Secretion in the Formation of Aqueous Humor as Revealed by the Influence of Arterial Blood Pressure on the Osmotic Pressure of the Aqueous, Acta physiol. Scandinav. **13**:81, 1947.

concentration of the blood and eliminates the differences between or reverses the osmotic relation of blood and aqueous humor. If the aqueous humor is taken with the use of local anesthesia, a higher molarity of the aqueous humor as compared with that of the blood is maintained. As an explanation, one may recall the findings of Margaria,[16] who, in Hill's laboratory, has previously shown that exercise raises the osmotic pressure of the blood up to 500 mm. of mercury by production of metabolites.

I had the opportunity to estimate the molar concentration of the aqueous humor, and at the same time that of the blood serum, in 4 men. The technic of determination was the same as that used for the lacrimal fluid. The samples were taken simultaneously—the aqueous humor with the use of local anesthesia and the sample of blood from the femoral vein. The molarities of the aqueous humor and the blood serum were separately established. Table 2 shows the results. These findings, which are in complete harmony with those of Duke-Elder's research group,[13] show that the osmotic concentration of the aqueous humor in these 4 subjects varied from 160 — to 160 + millimoles of sodium chloride, the average being 160 + millimoles. The corresponding values for the blood were 155 + and 160 + millimoles of sodium chloride, the average 160 — millimoles.

COMMENT

The significant fact in these findings for our problem is the absence of any considerable difference in osmotic concentration on the two sides of the cornea. The cornea seems to be situated within an osmotic milieu, divided by the cornea itself, the two sides of which are of nearly equal pressure. There seems not to be present the greater osmotic force needed to move fluid across the barrier represented by the cornea.

Cogan and Kinsey [17] advanced the theory of fluid movements in the cornea "according to which water is held to be abstracted continuously from the anterior and the posterior surface by osmotic forces. The resultant state of hydration represents an equilibrium between the osmotic forces at the corneal surfaces." Thus, a state of deturgence is maintained which is essential for transparency of the cornea. They showed on excised corneas that a "normal state of hydration" can be experimentally established when the difference in osmotic pressure of 0.7 per cent sodium chloride existed between the two sides of the cornea. Such a great difference does not seem to exist in vivo. The conditions in vivo are radically different.

16. Hill, A. V.: Adventures in Biophysics, Philadelphia, University of Pennsylvania Press, 1931.

17. Cogan, D. G., and Kinsey, V. E.: The Cornea: V. Physiologic Aspects, Arch. Ophth. **28**:661 (Oct.) 1942.

Evidently great changes in the osmotic concentration of the lacrimal fluid occur, owing to steady evaporation from the wet surfaces of the eye. Therefore, the lacrimal fluid of the open eye as secreted is expected to be of higher concentration than the values found under the artificial conditions in the present experiments. The changes influenced by evaporation, however, do not seem to alter in any way the imbibition state of the cornea, the tension or any other physical characteristic of the eyeball. On the other hand, it is likely that during sleep, or with the eye under surgical dressing, the osmotic concentration of the tears is similar to that found in my experiments. Even if the evaporation is prevented for a longer period by keeping the eye closed or bandaged, no physical alteration of the cornea can be detected. Thus the corneal tissues seem to be able to tolerate changes in osmotic concentration of the tears, and the tolerance is about equal to the changes due to evaporation. Within this limit of tolerance osmotic changes do not seem to induce physical changes which might be due to active transport of fluid.

The tissue fluid of the cornea is believed to originate from the pericorneal capillaries; by diffusing through the entire corneal substance, it provides the cornea with its metabolic needs. It is obvious that the corneal metabolism raises the molar concentration of the entering fluid, as metabolites are smaller particles than their mother substances. Such an assumption is supported by the findings of Margaria,[14] who could show that metabolites, produced in the muscle during exercise, upset the osmotic equilibrium between blood and tissue fluid. The increased osmotic activity during exercise raises the osmotic pressure of the circulatory blood to that of 1.033 per cent sodium chloride solution. Of course, the metabolic activity of the cornea does not undergo such radical variations, although it can be assumed that it is considerable enough to raise the molar concentration of the entering fluid continuously. Should the molar concentration of this fluid be that expected as the filtration product of the blood, the corneal metabolism might raise it to the height of the concentration of the intraocular and extraocular fluids. In any case, the molar concentration of the tissue fluid in the corneal substance has never been estimated, and no definite conclusion can be drawn from theoretic considerations. Such considerations would allow only slight osmotic differences, or, rather, a maintained equilibrium. It is unlikely that there are higher osmotic differences within and without the corneal substance.

One comes to the conclusion that the ocular fluids examined seem to be in osmotic equilibrium, and there is no conclusive evidence that active fluid movement is maintained into, from or through the cornea by osmotic forces.

CONCLUSIONS

The purpose of the present investigation is to show that the osmotic activity of the lacrimal fluid is about 160 millimoles of sodium chloride per kilogram of water, roughly equivalent to a 0.9 per cent sodium chloride solution. Collyriums should be adjusted to this osmotic concentration.

The osmotic activity of the aqueous humor is very similar to that of the tears, both being slightly higher than that of the blood. According to these findings, there are no differences in osmotic pressure on the two sides of the cornea which could account for movement of fluid across the cornea in either direction. Similarly, it is unlikely that the osmotic conditions found can support a hydration theory of the cornea.

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BLINDNESS AMONG PRACTICING PHYSICIANS

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THE ADVENT of blindness in a patient who has previously enjoyed good vision never ceases to be distressing to an ophthalmologist. When such a situation occasionally arises in a medical confrère, the ophthalmologist's feeling of inadequacy is even keener, and the desire to be of service usually seems devoid of specifics. Though many lay and semiprofessional organizations for aid and instruction to the blind have developed valuable services and teaching programs, most of these do not touch the problem of a medical physician.

This study was undertaken after we had come face to face with such a problem. Medical and biographic literature were combed for records of physicians meeting this situation in the past and in the present. An extensive search was made, and all major institutions dealing with the blind in the United States were contacted in an effort to locate the unsighted physicians practicing in this country. In addition, two blind physicians of Ireland, known to one of the American physicians, were located. To these men, request was made for information concerning their problems, and all but one responded generously.

The purpose of this paper is to bring together pertinent details from the lives of physicians continuing medical careers after the loss of vision and to collect the fruits of their experience which may be of aid to others facing the same difficulty. Everyday problems, such as eating and cane technics, common to all blind persons, will be omitted, but specific aids and suggestions for professional work will be presented according to the experience of blind physicians. The first part is a survey of all deceased physicians, even though their deaths may have been in recent years; the second is concerned only with currently active physicians and presents the conclusions that can be drawn.

I. BLIND PHYSICIANS FROM HISTORY

The presently known roster of blind physicians dates from 900 A.D. and lists twelve men who have earned sufficient distinction to be recorded in history. Currently, there are in the United States at least seven additional physicians who are continuing their profession without vision. The

contributions of these men to medical science and care are of considerable significance. Of course, there are some to whom blindness has been insurmountable. Neither details nor statistics in regard to these men have been sought, nor has any attempt been made to establish the number of blind physicians active in other countries. It is hoped this survey will answer some of the questions of newly blinded colleagues and reduce the number who feel unable to continue in the face of such difficulties.

Since the publication of "Entre aveugles" in 1903, ophthalmologic students have had at least one source book of aid to the newly blind. "Entre aveugles" was written by the famous Parisian oculist Émile Javal shortly after the onset of his own blindness, "particularly," he stated,[1] "to serve men of the liberal professions who have just made the 'leap in the dark.'" This little classic was soon translated into many languages, and the American edition, translated by Edson,[2] appeared in 1905. Javal has left to us not only his many scientific papers, his vivid auto-observations on glaucoma (1901) and his ophthalmometer, but also this volume, which stands as a "first"[3] in its field. Only a few of Javal's mechanical devices, such as his tandem tricycle, have become outmoded, whereas the spirit of his counsel for living and working with others will remain sound indefinitely. This treatise should be familiar to all ophthalmologists.

A large number of the blind have long been active in fields associated with that of the regular physician. Massage has commonly been practiced by the blind in many countries. In Japan, from the ninth century until 1870, when laws were promulgated equalizing opportunity for the nonblind, the blind enjoyed practically a monopoly in the fields of acupuncture and massage. In China they have long had a reputation for occult powers and mystic healing. At one time the education of blind masseurs warranted some German makers of anatomic models in producing types on which the nerves, muscles and other structures were indicated in relief. Recently some unsighted persons have successfully established themselves as physical therapists. A relatively large number of the blind have attained economic sufficiency in osteopathic and chiropractic occupations, but are not included in this study.

One of the earliest known blind physicians was the famous Rhazes[4] (Ar-Razii, circa 860-932 A.D.), sometimes referred to as the "Galen of

1. Javal, L. E.: Entre aveugles, Paris, Masson & Cie, 1903.

2. Javal, L. E.: On Becoming Blind, translated by C. E. Edson, New York, The Macmillan Company, 1905.

3. "Lettre sur les Aveugles," 1749, written by the controversial French encyclopedist Denis Diderot (1713-1784), was of greater philosophic than medical importance, but did consider the blind man of letters and was instrumental in breaking down the social barriers which hampered the blind in the eighteenth century.

4. Sigerist, H. E.: The Great Doctors, New York, W. W. Norton & Company, Inc., 1933, p. 81.

the Arabians." His fame as chief of the large hospital in Bagdad and his literary acclaim as the author of nearly 200 penetrating treatises were well established before blindness overtook him. He was a court physician and was favored in his medical studies by financial and other beneficences from Prince Al-Mansur. The story of his visual loss is dramatic but conveys less of helpfulness than do the accounts of later physicians. Late in life his more scientific reasoning temporarily gave way to an interest in alchemy, and he compiled a large treatise on that subject. Rhazes presented this to the Prince in a heavy, ornamental edition, just as he had done his valuable "Liber medicinalis ad almansorem" many years before. The Prince granted full support to proceed with the outlined plans for large scale development of the project. Rhazes, however, was reticent about accepting the commission and suggested that actual accomplishment would not be possible. For presenting a worthless treatise—one in which even the author lacked faith—Rhazes was beaten. According to Jujul,[5] the Prince struck Rhazes on the head with his whip; according to Elgood[6] and Castiglioni,[7] the Prince ordered Rhazes beaten on the head with his book of falsehoods until either his head or the book should break.

Subsequently, his vision began to fail, and his eyes gave him considerable pain for several years, until all sight was lost. Both the exact nature of his ocular disease and the ensuing course of his fortunes are somewhat uncertain. He refused to be operated on by couchers because they could not answer his questions concerning the anatomy of the eye. He continued to be sought out by pupils and probably endeavored to continue medical consultations, but with the loss of court favor his immediate prestige declined. He persevered in the preparation of the most exhaustive of his known writings, "al-Hawi," or "Liber continens" as it was later known in Latin translations. This enormous compilation of tenth century Mohammedan knowledge was not completed by the time of his death, but his pupils, fortunately, finished the work soon thereafter. Though he had occupied the highest pedestal in Arabian medicine and was to become a central column in medieval medicine, his last days were spent in financial adversity.

Somewhat more encouraging, though known in even less detail, is the long life of a later physician in Bagdad, Habatallah Ibn Malka,[8] who lived in the twelfth century. This Jewish philosopher, physician and

5. Jujul, I., cited by Robinson, V.: Pathfinders in Medicine, New York, Medical Life Press, 1912, p. 35.

6. Elgood, C.: Medicine in Persia, New York, Paul B. Hoeber, Inc., 1934, p. 38.

7. Castiglioni, A.: A History of Medicine, ed. 2, New York, Alfred A. Knopf, Inc., 1947, pp. 267-270.

8. Sarton, G.: Introduction to the History of Science, Baltimore, Williams & Wilkins Company, 1931, vol. 2, p. 307.

astronomer wrote in Arabic a distinguished summary of galenic anatomy and was reported to have cured psychopathic patients by suggestion. The cause of his blindness is unknown, but his chief work, "Mo'tabar," a treatise on logic, physics and metaphysics, was composed and dictated to his followers after he became blind. Ultimately he also lost his hearing but lived until the age of 80, when he died with elephantiasis.

The French physician Bourdelot was a less well known member of the large procession of physicians who attended Louis XIV. Sir Stewart Duke-Elder [9] relays a fragmentary account of this physician, who apparently died in the early eighteenth century. Bourdelot had bilateral glaucoma but probably continued in his professional capacity after becoming blind. At the end of the seventeenth century, ophthalmic pathology was even more obscure than it is now, and the great Maitre-Jan (1650-1730) contended that both glaucoma and cataract were lenticular diseases. The blind eyes of Bourdelot were subjected to an anatomic examination by young Michel Brisseau (born circa 1673; died 1743), who demonstrated that the lenses were grossly normal. Fortified with this additional evidence, Brisseau presented to the Académie royale des sciences his now famous arguments [10] differentiating cataract, as a distinct disease of the lens, from glaucoma, which he thought to be a disease of the vitreous. Thus, the blind Bourdelot served medicine both in the years of his life and in the many years to follow.

Hugh James [11] (1771-1817), "the blind physician of Carlisle," England, shared with most blind doctors the advantage of obtaining his basic education while sighted. He studied surgery at London and Edinburgh and at the completion of this work, in 1796, settled as a surgeon in Whitehaven, England. Two years after beginning his practice, he had a severe ocular inflammation, apparently iridocyclitis. This was attended with such pain and visual impairment that he was forced to relinquish his practice of surgery. After a few years marked by exacerbations and pain, his vision improved enough so that he could return to Edinburgh for further studies in medicine. In 1803 he graduated as a physician and settled in Carlisle. Repeated flare-ups of his inflammation, however, were uncontrollable by the best oculists of London and finally deprived him of all vision by 1806. Notwithstanding his relatively short period in practice—three years—and the privation of vision, his success as a practitioner rapidly mounted. He was readily available for house calls to the rich and to the poor. His biographer notes that he was particularly penetrating in eliciting details of the patient's history, thus compensating for visual signs, of which he was

9. Duke-Elder, W. S.: Text-Book of Ophthalmology, St. Louis, C. V. Mosby Company, 1940, vol. 3, p. 3282; personal communication to the authors.

10. Brisseau: Nouvelles observations sur la cataracte, Tournay, 1706.

11. Wilson, J.: Biography of the Blind, Birmingham, England, 1838.

deprived. His life was prematurely terminated by an acute inflammatory illness contracted while attending a patient. His fellow citizens, to whom he had become endeared during fourteen years of practice, erected a monument to him, on which is inscribed, in part:

> To the memory of Hugh James, M.D., who practiced physic with eminent skill, for many years, in this city. Providence largely recompensed the loss of sight in early life, with talents which raised him to a distinguished reputation in his profession, and even more abundantly blessed him with a disposition ever prompt to succor poverty and pain.

The field of psychiatry is particularly suitable to sightless physicians, and Dr. Henry Mills Harlow [12] (1821-1893) was one of the New England pioneers in the institutional aspects of this field. He attended medical lectures at Harvard, graduated from Berkshire Medical School in 1844 and then spent six years of study as assistant physician in the "insane asylums" of Vermont and Maine. In 1850 he was appointed superintendent of the Maine Insane Hospital. While serving in this capacity, he had bilateral iritis, which slowly destroyed his vision. Whether or not he was totally blind is somewhat uncertain. Notwithstanding a visual loss of at least severe degree, he served one term as president of the New England Psychological Society and in 1861 became president of the Maine Medical Association. After thirty-eight years of institutional work, he relinquished his superintendency but still delighted in frequent visits to the hospital and continued to see patients in consultation. He continued in this semiretirement for seventeen years and died suddenly, while dictating a letter, in 1893.

Hugh Lennox Hodge [13] (1796-1873), of Philadelphia, was one of two physicians known to have continued actively in the practice of obstetrics after the loss of vision. Hodge pursued his education against financial difficulty and obtained his degree of Doctor of Medicine from the University of Pennsylvania in 1818. His next several years were spent in surgery, but the onset of a slowly progressive visual impairment, apparently optic nerve atrophy, directed his attention away from surgery, toward obstetrics and gynecology. Year by year his skill and practice grew, but his vision continued to become poorer. While working with William Dewees, his predecessor in the chair of obstetrics at the University of Pennsylvania, he became interested in problems of the displaced uterus, and in the early 1830's he perfected the lever pessary widely known by his name. With further decline in his vision, he turned more toward gynecology, but his name remains associated

12. (*a*) Kelly, H. A., and Burrage, W. L.: American Medical Biographies, Baltimore, The Norman Remington Company, 1920, p. 493. (*b*) Spaulding, J. A.: Necrology of Henry Mills Harlow, Tr. Maine M. A. **11**:363-366, 1893-1894.

13. Kelly and Burrage,[12a] p. 535. Goodell, W.: Biographical Memoir of Hugh L. Hodge, M.D., L.L.D., Philadelphia, Collins (Printer), 1874.

with many obstetric contributions, such as the Hodge plane, the Hodge forceps and the Hodge craniotomy scissors. In 1835 he was elevated to the professorate and served it well with many original investigations. Utilizing his last vestiges of sight, he published in 1860 his textbook on "Diseases Peculiar to Women." Because of his blindness and the long tenure which his advanced age had afforded, he relinquished his university position in 1863 and accepted the title of professor emeritus. With the constant aid of an amanuensis, he turned to the completion of his greatest work, "Principles and Practice of Obstetrics," which was published in 1864 and was greatly acclaimed in America and abroad for its masterful illustrations and original approach. He realized the value of profuse illustrations in teaching material, and yet to be certain of their technical correctness posed a difficult problem for a blind man. To solve this, he utilized photography—then an infant science—and held with his own hands specimens from his extensive collection, carefully fitting together pelves and fetal heads or demonstrating pathologic conditions, while the camera man made long exposures.

Dr. Hodge continued to see many private patients and at the hospital still answered frequent requests for consultation. He retained a keen insight and sympathetic understanding when helping younger physicians out of difficult situations. At the age of 77 he died unexpectedly, of occlusion of a coronary vessel, following a day of intensive activity, visiting many patients and preparing an article on cephalotripsy.

The other obstetrician was Dr. Vosy,[8] of Choisy-le-roi, France, in the late nineteenth century. Dr. Vosy apparently had established himself in obstetric practice before becoming blind, but continued his activities both as an attending physician and as a consultant. His contemporary, Dr. Javal, remarked[8]: "It appears that for certain young women the blindness of Dr. Vosy is even an additional reason for employing his services."

The visual loss of Dr. Thomas Rhodes Armitage[14] (1824-1890), of London, is of real and historical importance to all the blind of England. He received an excellent early education in Germany, followed by medical studies in King's College. Subsequently he studied in Paris and then in Vienna, where began a lifelong friendship with the great diagnostician Josef Skoda. His unusual abilities while at King's College had attracted the attention of Dr. Robert Bentley Todd, and on his returning to London he rapidly acquired a fine practice of his own and assisted this distinguished internist and author. Dr. Armitage published in 1852 a sound volume, entitled "Hydrotherapy as Applied to Acute Disease."

14. Obituary: Thomas Rhodes Armitage, Brit. M. J. **2**:1039-1040, 1890. Biography of Dr. Thomas Rhodes Armitage, London, National Institute for the Blind, 1950, to be published. Encyclopædia Britannica, ed. 14, Chicago, Encyclopædia Britannica, Inc., 1939, vol. 3, pp. 724 and 731.

Dr. Todd's death, in 1860, followed only by a few years the entrance of Dr. Armitage into practice, and previous arrangements were then carried out for the younger man to step into the office and practice of Dr. Todd. Not only were his capabilities highly deserving, but this relationship enhanced his prestige and placed him further along the way of a distinguished career, at the age of only 36.

Within another few years his sight, which had never been good, failed almost completely and he felt constrained to relinquish clinical practice. This never lessened his deep interest in medical matters, but thereafter he apparently rendered no further medical care for remuneration. He continued to treat many of his friends and the poor, but his efforts were most vigorously turned toward the improvement of conditions for the blind, particularly the educational and institutional aspects. In 1868 he founded the British and Foreign Blind Association, parent organization of London's now world-famous National Institute for the Blind. As one of the originators of the Royal College for the Blind (Upper Norwood), he gave not only of time and talent but at least 40,000 pounds in financial support. For the benefit of those who had attained little education prior to blindness, he wrote a volume entitled, "The Education and Employment of the Blind." This was well received and went into a second edition.

Though his vision was so poor that his personal diary was kept in braille from 1846 on, a vestige of travel vision remained for many years, before he became totally blind. Late in life he also became deaf, but this did not curtail his activities or energies, and in 1890 he died suddenly, after injuries sustained when his horse fell and rolled over him. His keynote was always that the blind should become self reliant and self sufficient by their own exertions.

The blindness of Émile Javal[15] (1839-1907) is ironical in that one who had devoted his life to visual sciences should become totally deprived of vision. Javal's reputation as a thinker and investigator was foreshadowed in his student days at the University of Paris, during which he published sixteen articles on astigmatism and orthoptics before graduating in medicine. Within a few years of his graduation he was made the first director of the newly created Ophthalmic Laboratories at the Sorbonne and soon gained international fame for his work. At the relatively early age of 45, he was elected to the Academy of Medicine—a signal honor for an ophthalmologist—but at the same time there developed the first symptoms of glaucoma. In the following year (1885) both a sclerotomy and an iridectomy were done on his right eye, but vision was totally lost within a few months.

15. Lebensohn, J. E.: Louis Émile Javal: A Centenary Tribute, Arch. Ophth. **21**:650-661 (April) 1939. Obituary of Émile Javal, Lancet **1**:471, 1907. Obituary of Émile Javal, Brit. M. J. **1**:238, 1907. The American Encyclopedia and Dictionary of Ophthalmology, Chicago, Cleveland Press, 1913-1921, vol. 9, pp. 6709-6713.

Vision in the remaining eye continued slowly to fail for fifteen years in spite of the constant use of pilocarpine, and only a modicum of sight was left when, in 1900, he went to Priestly Smith of Birmingham, England, for an iridectomy. This effected a temporary respite, but five months later he was totally blind. On his returning to Paris, Javal insisted on a cervical sympathectomy, which proved to be a long ordeal, without benefit.

Soon after this operation he resumed a limited amount of ophthalmic consultation, with the aid of his assistant, Sulzer, who had been with him for twelve years. Tscherning undertook the directorship of the Laboratories, but Javal, as "honorary director," continued to steer in some degree the work being carried on at the Sorbonne. His most immediately engaging task, however, was the study of means by which the lot of those who had lost their sight in the midst of active life could be eased.

Within a year he presented to the Academy of Medicine an ingenious writing board for the blind, free from the usual types of guides which interfere with finger motion. Within three years the collected fruits of his studies appeared in the now famous volume, "Entre aveugles."

The mastery of braille may be a great asset to blind children, but to a physician who has enjoyed the speed and selectivity of conventional reading, Javal suggests this cumbersome process only for brief notes, indexing or as "an incomparable bedfellow in case of insomnia."

Javal lived the essence of his quotation from M. Riggenbach, blind professor of theology at Basel:

> The adult becoming blind ought to continue his profession in every case in which it is possible and not to allow himself to be stopped by the difficulties at the start. The blind can find satisfaction in existence only if he does not live for himself alone.

Javal's plea to other ophthalmologists not to leave the imminent blind in unreasonable hope or attempt consolation by placebo treatment, but rather to "prepare them little by little for their fate" remains a valuable dictum, gaining for a physician precious time in which to reorganize his work.

The contributions by Javal to professional literature also continued after his blindness. Two years before his death, his volume "Physiologie de la lecture, de l'ecriture, et des signes en general" appeared, and the first printing was exhausted in three months. The Ophthalmological Society of the United Kingdom invited him to give the Bowman Lecture for 1907, but this final honor had to be refused because of an exhausting abdominal illness. Javal died in 1907 of gastric carcinoma. In order that Priestly Smith might not feel that his services were entirely unrewarding, Javal directed that the eye on which Smith had operated be sent to him. At autopsy, Tscherning performed the enucleation and dispatched the globe to Birmingham.

Blindness to Javal was like infection to Lister; he methodically set about to overcome it, and all those to follow profit by his endeavor.

The blindness of Dr. Gilbert Prout Girdwood [16] (1832-1917), of Montreal, did not occur until this versatile and venerable physician, surgeon, roentgenologist and chemist was nearly 80 years of age. In 1902 he had accepted a change in his status from professor to professor emeritus on the McGill University Faculty of Medicine but continued an active participation in his fields of medical interest, even after his loss of vision. Utilizing the eyes of his wife and daughter, he made an investigation into the effects of carbon dioxide in coal gas on the public health in England, the United States and Canada. The results of these studies were published by the Royal Society of Canada shortly before his death, which occurred at the age of 85 years.

One of the two blind physicians to have been listed by "Who's Who in America" was Dr. Arthur Washington De Roaldés [17] (1849-1918), of New Orleans. Dr. De Roaldés was well educated in letters and medicine, both in Louisiana and in France. Caught abroad at the outbreak of the Franco-Prussian war, he served, as did young Dr. Javal, with the French and was decorated for bravery. He returned to New Orleans in 1872 and became a progressive surgeon in chief to the Charity Hospital in 1880. In 1887 he began a special study of otolaryngology in the major European clinics and returned in 1889 to establish the still flourishing Eye, Ear, Nose and Throat Hospital of New Orleans. The following year he was elected to the chair of otolaryngology in the New Orleans Polyclinic (now Tulane University of Louisiana Postgraduate School of Medicine) and steadily rose to be one of the most prominent otolaryngologists in America.

In August 1896, while on an annual visit to France,[18] he was stricken with optic neuritis. The most distinguished oculists of Paris and Vienna were unable to help him, and by the time of his return to New Orleans, in November, he was completely blind. He continued, however, very actively in teaching, consultation and other medical affairs for more than fifteen years. With the aid of another physician and competent assistants, he maintained an office practice, supervised the administration of the hospital foundation and even participated in surgical procedures.

A tribute to his skill is found in the story of a mastoid operation in which an associated surgeon had proceeded as far as he thought would

16. Obituary of Gilbert Prout Girdwood, Brit. M. J. **2**:814-815, 1917. Memoriam to Dr. Gilbert Girdwood, Tr. Roy. Soc. Canada, **2**:7-10, 1918.

17. Louisianians and Their State, New Orleans, Louisiana Historical and Biographical Association, 1919, pp. 97-98. Kelly, H. A., and Burrage, W. L.: Dictionary of American Medical Biography, New York, D. Appleton & Company, 1928, p. 320.

18. Personal communications from members of the family.

be safe for the patient. Dr. De Roaldés palpated the area and advised, "I would go deeper here." Further incision was made, and the necessity of the additional incision, exposing diseased bone, was demonstrated. His continuing interest in national medical affairs is evidenced by his participation in the American College of Surgeons and, in 1906, ten years after becoming blind, his election to the presidency of the American Laryngological Association.[19]

He received citations and honors as a humanitarian and a physician from his American colleagues and from the governments of France, Italy, Russia, Spain and Germany, which sent gifts to the hospital in appreciation of medical attention rendered their indigent sick. His contributions to otorhinolaryngologic literature were frequent both in American and in French journals and continued to appear even after he became blind. In 1911 ill health, but not blindness, forced him to retire from active practice, only seven years before his death.

In contrast to the many who have continued practice after becoming blind in adult life, Dr. Robert H. Babcock [20] (1851-1930), of Chicago, lost the vision of both eyes at the age of 13 years. Robert's eyes were destroyed by a toy bomb made with the powder of an old shotgun shell during Civil War days, when children throughout the nation were playing soldier. Blindness became complete almost immediately. To obviate the danger of a pampered home life and speed the development of self confidence, his parents, though able to afford private tutors, wisely sent him to a blind institution, where he learned that special advantages should not be sought by self-reliant persons. Later, in preparatory school, his roommate read lessons to him and described scientific experiments as they stood side by side in the laboratories. He said, "The real handicap I had to overcome was not blindness; it was the danger of thinking that blindness was insuperable." There were, of course, periods of "deep despondency," when the future seemed "to stretch so dark and hopelessly" before him that he even contemplated suicide.

Through applied effort, he acquired an unusually good memory and studiously avoided mannerisms of the blind, even to the extent of memorizing the sequence of bills in his wallet, so that he could pay irregular amounts without hesitancy. In college, he followed a literary course and then attended the medical college at Ann Arbor, Mich., for two years. Subsequently, he went to the Chicago Medical College, where he mastered cadaver dissection by touch and won his degree of Doctor of Medicine in 1878. He studied further at the College of Physicians and Surgeons, in New York, where during lectures on

19. Memorial, Arthur Washington De Roaldés, Tr. Am. Laryng. A. **41**:270, 1919.

20. Most of this material has been obtained from personal papers loaned by the Babcock family, through the courtesy of arrangements made by Dr. E. V. L. Brown and Dr. N. C. Gilbert, of Chicago.

osteology he would keep specimens in his hands and follow the discussions better than most of his sighted colleagues. Here he obtained a second degree in medicine in 1879 and was one of ten honor men in a class of 130. In the same year he married a cultured and understanding woman, who became a great help and ever available reader during the rest of her life.[21] She traveled abroad with him for three years of final study in Munich, Berlin, and Leipzig.

After nine years of such careful preparation, he opened an office in Chicago, employing an assistant, who, Dr. Babcock said, had practically nothing to do but read to him during those early years. As his practice grew, subsequent assistants were drawn from the ranks of younger physicians and helped out in cases in which sight was essential. In common with other beginning practitioners, he found that it was nearly ten years before his earnings were enough for him to realize the goal of self dependence. During those years he published many papers, secured a teaching appointment in the College of Physicians and Surgeons in Chicago and was later appointed attending physician at Cook County Hospital.

His private practice and teaching reputation now grew rapidly. Appleton and Company requested him to write a textbook on the cardiovascular system; this spurred him to purchase one of the first typewriters sold in Chicago. Using this new machine, he worked on the book steadily, mostly in the evenings, for five years. Mrs. Babcock, in addition to raising their two children, helped with the revision of copy, and in 1903 his "Diseases of the Heart and Arterial System" appeared, with the author's credentials now dignified as professor of clinical medicine. The following note extracted from family papers reflects the international response to this work.

I, West Franklin Street
Baltimore, Md., Jan. 2nd, 1904

Dear Babcock,

I hope you read Gibson's review of your book in the November or December number of the *Edinburgh Medical Journal*. I had a talk with him about your book in the summer. He was greatly pleased with it, as of course we all are. There was another good review in the *Dublin Journal* I think, but I cannot be certain. I had intended to send you a postal card about it but neglected it.

I send you a photograph with great pleasure. With the best wishes for the New Year,

Sincerely yours,
(s) W. Osler.

P. S. You must get one of the Chicago men to put your name up for our Association of American Physicians if they have not already done so. I am on the Council and cannot or I would do it with pleasure.

21. Personal communication from Dr. James B. Herrick, Chicago.

Though he had learned to read braille as a youngster, Babcock, like Javal, disliked its slowness and the cumbersome size of braille volumes. He did enjoy raised markings for playing cards and at times used specially prepared syringes with etched markings on the pistons, which enabled him to measure by touch the volume of solution withdrawn. To aid in taking the pulse rate, he had his watch fitted so that the second hand produced a distinct click every thirty seconds.

As president of the Society of Internal Medicine, he conducted large meetings with keen sensitivity to proceedings throughout the room. Apparently, he memorized each program and would introduce successive speakers without aid from notes or other persons. His gestures were sure, and his manner was alert and forceful. Immaculate dressing further belied his blindness.

In 1907 he published another volume, entitled "Diseases of the Lungs," which was warmly received for its clarity and organization. His "Diseases of the Heart" went into a second edition, and he also wrote a volume for lay readers, "Your Heart and How to Take Care of It."

The greatest disturbance to Dr. Babcock's usual poise followed the death of Mrs. Babcock, in 1920. Many professional honors continued to be paid to him, but in 1928 a serious heart attack precipitated his retirement, after forty-six years of vigorous practice. He died in 1930.

Because of increasing emphasis on microscopy and other visual aids in medical school, he did not encourage young men with his handicap to begin the study of medicine, but to those acquiring blindness his maxim was, "Never indulge in self pity."

II. CONTEMPORARY BLIND PHYSICIANS

The rapidly increasing use of visual aids in medicine has made it more difficult for scientific physicians of today to continue in medicine without vision. On the other hand, the generally increased social consciousness of this era has reflected to the advantage of all handicapped persons. Though most surgical specialties and some medical fields, such as dermatology, are rather well precluded, a large selection of avenues still remains accessible to the blind physician who is resourceful.

The material to follow concerns currently active physicians only, and is drawn almost entirely from personal communications. The names and certain identifying data with regard to these physicians have been omitted, in consideration of their privacy. Should it seem important for another physician to communicate with any of them, we are willing to convey such a request to the person in question for further consideration, as he may see fit.

Such value as there may be in this section is entirely to the credit of these physicians, who have been so generous in contributing from their personal experience.

Internist and Endocrinologist.—"The disadvantages of attempting to work as a physician without the benefit of vision are too obvious to require comment," this physician writes, but he has practiced and taught under such conditions for the last twelve years, with a vigorous schedule of activities which suggest that these disadvantages can be minimized. Beginning with high myopia in childhood, he had always been troubled with his eyes. During adolescence his myopia increased to about 12 D. but did not progress so far as to interfere with his medical education, in a large eastern university.

After four years of residency and research fellowship, he married a pediatrician on the same hospital staff. At the completion of his training he opened downtown offices for the practice of internal medicine and endocrinology but continued to devote about half his time to teaching, ward and clinic work at the hospital of his university.

This arrangement had become increasingly satisfactory, when, about eight years later, a slight head trauma precipitated a retinal separation and macular tear in the left eye. The best ophthalmologists of the country felt that surgery would be of no avail, and all vision was soon lost in that eye. Simultaneously, vitreous opacities began to develop in the other eye; but vision temporarily remained adequate, and he even obtained certification from the American Board of Internal Medicine during this period. Unfortunately, cataractous changes supervened in the good eye about five years after the loss of the first eye, and within another two years spontaneous retinal separation imperiled the remaining vestiges of sight. Attempted surgical treatment was unsuccessful, and all vision was lost by the age of 41.

After a three month period of recuperation and rest, he moved his "center of operations" to the university hospital, where he continues an active private practice and a full schedule of teaching duties in endocrinology. Fortunately, his wife was able to locate her office nearby in the same building, and they drive together back and forth from their suburban home. In addition to raising two sons, they have both steadily advanced in their work at the university, where he is now an associate professor of clinical medicine and director of the endocrinology clinic.

Since his blindness, he has written or collaborated in more than twelve published medical papers, has been active in the American College of Physicians and has addressed various societies from time to time throughout the country. Occasionally he goes to patients' homes, but practically all his work is done at the hospital. The widow of a former colleague, who is versed in medical topics, reads to him about three nights

a week, and, of course, his wife has been of invaluable assistance. Because of the little time available for nonmedical reading and the greater speed obtainable through "Talking Books," he has never thought it worth while to learn braille.

On the asset side of the ledger, he believes there has been some increase in his ability to concentrate, and he is convinced that there is a "real increase in auditory sensitivity." "The latter," however, "operates as a two-edged weapon, since it greatly increases [his] annoyance at obtrusive noises." Working against blindness, he feels," has been helped by possessing a rather lively imagination of the visual type."

Psychiatrist.—This physician had won his degree of Doctor of Medicine at the University of Zurich and had nearly completed two years of residency in psychiatry when chronic chorioretinitis of unknown cause began the destruction of his vision, at the age of 25. This condition progressed to total blindness by the time he was 31. After losing several years in a fruitless attempt to "conserve" his sight, he entered practice because of the need to do something useful with his life.

In the thirteen years that he has been in practice, the greatest handicap he has found has been "that imposed by a skeptical world." His practice, nonetheless, has steadily grown, and he is now centrally located in one of the largest and most competitive eastern cities in this country.

He keeps abreast of literature, with the aid of readers, and finds that most persons with native intelligence can easily make up for unfamiliarity with psychiatric jargon and soon become helpful associates. Unmarried and without dependents, he usually travels alone and prefers rush hours in order that others may be about in case of need. Traveling unattended to and from his office is "not pleasant, but it is essential to get there, and one may therefore wave this difficulty aside."

Regius Professor of Medicine; Former President of the British Medical Association—This physician, of Ireland, had been myopic from early life, but even though his refractive error progressed to about 11 D., he was able to "qualify in medicine," at the age of 22. After a few years he became extremely busy with hospital and consultant medical practice. His position of leadership in medical affairs and his reputation as a practitioner steadily advanced.

At the age of 42, spontaneous retinal separation occurred in the right eye, and, in spite of the best known medical measures and an operative attempt at repair, the eye went on to complete blindness in a short time. Five years later separation occurred in the other eye, and he was again laid up for several months, until a measure of improvement was achieved. At this time he felt constrained to relinquish his hospital appointments but, with the help of an assistant, continued to see a fair number of

patients in his "study" and was kept busy with consultation work. Because of further separation in the remaining eye, three years after its original involvement, he went to Zurich, where a series of operative repairs were attempted. These measures, however, led to chronic iridocyclitis, necessitating enucleation within the year.

Thus, at the age of 50, he returned to Dublin totally blind. With the aid of a secretary, who read blood pressures and helped in other minor ways, he resumed the care of patients in his study and undertook some consultations in private homes.

Now, at the age of 70, he is still fairly active as a consultant, and his opinion is regarded as valuable. He has extended his attention from the medical staff of his usual hospital to include its board of governors. He currently serves as chairman of this board and, in addition, sits on the boards of three other hospitals. He has published a short history of one of the famous old Dublin hospitals, a pamphlet on the work of a tuberculosis sanatorium and several shorter medical papers since becoming blind.

He has been unusually active in medical organization, serving on the executive councils of the Medical Association of Ireland, the Medical Research Council and the Medical Registration Council, and as president of the Royal College of Physicians in Ireland. The height of his organizational work was probably reached in the last decade, when he was elected president of the British Medical Association. On official medical missions he has traveled as far as Canada and Jerusalem, always taking with him his wife, who acts as his secretary and reader. He has assiduously developed his auditory memory. Prior to attending meetings he thoroughly fixes in mind the entire agendum, so as to conduct or follow the proceedings without assistance. Utilizing conventional secretarial methods, he now does no writing other than that of medical prescriptions and his signature. Since the loss of vision, he has also retained his position as regius professor of medicine in the medical school with which he has been associated for many years. This involves the reading of candidates' theses for the degree of Doctor of Medicine and the conducting of oral examinations.

"My feeling is that any doctor who becomes blind can, with determination, carry on his life."

Psychiatrist Specializing in the Neuroses and Psychoanalytic Method.—At the age of 22 this physician graduated from Harvard Medical School and, after internship, entered general practice and industrial surgery. Three years after he opened practice, the first symptoms of glaucoma simplex appeared, and their progression was uncontrolled by pilocarpine. Two years later bilateral iridectomy was performed, but the condition in the right eye went on to absolute glaucoma, requiring enucleation in another two years. The remaining

eye continued to deteriorate over the next five years. Despite further surgical care, the last traces of vision were destroyed by intraocular hemorrhages and retinal separation, just eleven years after he entered practice.

During the last year in which some vision remained, he began the study of psychiatry, both in Boston clinics and by special arrangements in New York. During this period of intensive preparation for changing his type of practice, he utilized the aid of two readers. Since entering this specialty, he has concentrated on therapy of the neuroses. His wife, also a psychiatrist, helps in situations requiring sight, but, in general, he says, "My blindness is only a slight handicap and sometimes a benefit, for patients often say that they can talk to me more easily because I cannot see them." He feels that blindness may further be an aid in facilitating more complete concentration on the problems of the patient, especially during analysis.

Nineteen years ago he learned braille but found it of slight use and now employs it very little. By utilizing conventional methods of dictation and secretarial assistance, he has found no need for special sound-recording devices. The "Talking Book" provides considerable relaxation, he finds, but skilled readers afford him the most satisfaction because of their ability to abridge and skim as they learn his tastes. Since the loss of vision, he has enjoyed a "better medical practice" than during the decades prior to his blindness.

Chief Medical Adviser, State Industrial Accident Commission.—This physician developed Eales' disease at the time of his graduation from Harvard Medical School. Despite rapid progression to blindness in the left eye, he completed his training with a year of pathology, two years in general surgery and two more in orthopedics before his other eye became involved. Because of repeated hemorrhages, he decided not to enter active practice, but to work toward a position which he knew he could hold after becoming totally blind. He became a medical examiner for his home state accident commission, personally performing examinations and making disability evaluations for a period of four years, during which time the vision in his right eye further deteriorated.

Through this service he earned promotion to the rank of medical adviser to the commission, and his duties became comparable to those of medical adviser to an insurance company, consisting in passing on disability evaluations of other examiners, passing on requests for authorization of surgery, determining relations between trauma and preexisting lesions, and the like.

Psychologically, the fight for vision in the period of partial sight was so great that he felt unable to initiate any preparation for blindness. In the everyday matters of retraining, he feels that "only a few months"

are required to accomplish the adjustments, and that they can be made "more extensively and more perfectly when one is blind than while one is still sighted."

During the years of failing vision, and since the onset of total blindness, he has published several articles on this phase of medicine, has written a capable monograph on "Injuries of the Carpus," now in its second edition, and has addressed local and national medical meetings in various cities. During the past year he was elected to the American Association for Surgery of Trauma.

He has recently developed a more extensive use of the disk type of sound recording. In addition to a conventional dictaphone for ordinary letters, he uses a disk recorder [22] in his office to take down important parts in telephone conversations, similar to the way in which a pad and pencil might be used. At home he uses another disk recorder to abstract articles as they are read to him, or places it by the reader for complete recording of more important material. He is thus maintaining a medical disk library, to which he can refer without assistance. He uses braille to index the disks, as well as for other short note purposes, and for this purpose he considers it "an absolutely necessary evil."

In the preparation of articles, he dictates a rough draft on the recorder, then listens to it slowly on the transcriber and redictates it along with editing, as needed. After two or three revisions in this manner, the final draft is dictated on to the permanent disk. At medical meetings he delivers his papers without the use of notes.

Despite total blindness for a period of six years, this physician has steadily progressed in his field and is now chief medical adviser to the commission. He enjoys a rounded home life and participates in many recreations with his two children. With Dr. Babcock, he admonishes persons facing this handicap "carefully to avoid self pity." "To speak perfectly frankly, blindness is only a damn nuisance and does not prevent a person from doing anything worth while if he is willing to go after it hard."

General Practitioner, Ireland.—Among the known physicians continuing practice without sight, this man is the only general practitioner. He began his medical training with emphasis on obstetrics and in 1893 became a licentiate in midwifery. The following year he qualified in medicine with the degrees of M.B., B.Ch. and B.A.O. (Bachelor in the Arts of Obstetrics), and in 1897 he earned his degree of Doctor of Medicine. He entered general practice and soon obtained an appointment as a dispensary doctor.

22. Recorders and transcribers manufactured by Sound Scriber Corporation, New Haven, Conn., have been used because of the apparently greater mechanical durability of both the instruments and the recordings.

His eyes had been myopic from early life, and a few years after the turn of the century there developed a spontaneous retinal separation, which led shortly to loss of all vision in that eye. He continued active practice, however, and in 1917, while entrained for duty with the British Army, sustained a retinal separation in the remaining eye. This curtailed any further military service, and on his returning to Ireland he relinquished his dispensary appointment, as well as surgical and obstetric practice. During the next four years his remaining vision gradually declined, and he learned braille in anticipation of the total loss of vision which was to occur by 1921. Though the blindness was somewhat of a blow to his self confidence, he continued to see patients, with the regular assistance of a nurse. His practice now is largely confined to chronic medical problems. Prior to the loss of vision he had practiced about twenty years, but now, at the age of 77, he has outstripped this period of service with twenty-eight years of unsighted practice.

Internist and Diabetologist.—The immediate problems caused by visual loss are best evaluated by physicians who have more recently faced such an event. The blindness in this case became total only about three years ago and is the most recent in our survey. This physician was born abroad, came to America with his family at the age of 12 and later earned his A.B. and M.D. degrees from a large western university. Within a few years he began private practice in the city of that university, and he was subsequently appointed to the medical faculty of his alma mater. He organized an outpatient clinic for diabetes and has remained directly in charge of it, along with teaching duties.

After fifteen years of increasingly successful practice and university affiliation, there developed a thrombosis of the central vein of the retina. All vision was lost in the affected eye within two months. About three weeks later thromboses developed in the branches of the vein of the other eye, and, despite the best therapy, the course continued to be downhill. During the few months of unilateral impairment he maintained an intensive schedule, but after involvement of the second eye he discontinued his practice. Within three months, however, the condition seemed stabilized, and a vestige of travel vision remained. He resumed duties at the diabetes clinic and the next month returned to his office on an experimental basis, with the aid of his brother, a general practitioner, who transferred his nearby small town practice to the blind man's office. Unfortunately, a retinal separation shortly thereafter presaged the final loss of all vision, which occurred within ten months of his return to practice.

There were periods of uneasiness about ability to practice, occasional feelings of bitterness and even fear at the prospect of darkness. In the routine matters of continuing practice, he has found the assistance of an intelligently understanding nurse-secretary to be a great asset. Such

a person, also doubling as chauffeur, reader and hospital roundsman, lends a uniform element to his assistance. She amplifies his histories and physical examinations by describing the skin, the throat and any visible irregularities. Further necessary inspections, such as those of the eye, nose, vagina or rectum, are made by his brother or are referred to indicated specialists. His confidence, his feeling of usefulness and even his patients began to return. After one or two apparently "duty calls," however, a certain percentage of his patients, though remaining friendly and solicitous, did not return for further care. He considered this due to the illogical premise of many sighted people that blindness confers an "utter helplessness on the person so afflicted," and realized without resentment that he would have to "prove" himself.

In time new patients came, and the number of diabetic patients increased as colleagues recognized his special abilities and referred more of their problems. Even many of the previously defecting patients returned as the word of his capability spread.

Except by improving his interpretations of sensations received through touch, hearing and smell, he has utilized no special aids to practice. Since his blindness, he has contributed literature to the field of diabetology, participated in the conduction of postgraduate seminars, traveled with his wife to medical meetings in various parts of the country and maintained an active role in community affairs. Today, an assistant professor of internal medicine, he now finds, "I have more time for thought than I had prior to my blindness, and I use this to advantage in thinking out the problems of correlation and interpretation of the findings. As a result . . . my diagnoses have been correct in a larger proportion of cases than heretofore. . . . One's failures derive not so much from what one cannot see as from what one does not look for."

SUMMARY AND CONCLUSIONS

A survey has been made of the successful adjustment of physicians, historical and contemporary, to visual loss. Data from 12 blind physicians of the past and 7 currently active blind physicians are presented. The personal nature of this study makes it probable that some cases have been missed; any omissions are unintentional.

The average age at onset of blindness, as determined from 14 cases in which the records were adequate, was 45 years. The average length of practice of these men, 7 of whom are still active, after the advent of blindness has been sixteen years, or a total of two hundred and twenty-four physician years.

The main conclusion to be drawn from this survey is that loss of vision in a physician, while imposing considerable difficulties, is not insurmountable, and that he should be encouraged to continue in the

medical field in spite of initial hardships. The farther a physician has advanced in his medical career, the less difficulty may be anticipated in reorganization of his work. The period of ophthalmic illness usually preceding total blindness should be used under the frank and honest guidance of the ophthalmologist to prepare for the eventuality of blindness. Three of the living physicians have mentioned the impossibility of preparing themselves psychologically or in matters of routine blind technic, such as learning braille and cane walking, but have availed themselves of this period to reorganize the goals of their careers in view of approaching blindness.

In mental outlook, the active avoidance of self pity by continued efforts toward self reliance is fundamental for a useful adjustment. In achieving self dependence, the blind physician must be prepared to "prove" the value of his services on the "open market." Mechanical aid gadgets are far less important than the skilled assistance of understanding associates. The busy physician, whether sighted or not, will progressively delegate mechanical tasks to his trained assistants.

For medical reading, the trained professional reader, regularly engaged on a salary basis, affords most satisfaction, although the role of the physician's wife or an intimate member of the family must not be underestimated. The use of braille is of little value to the physician except for short notes and in indexing. The modern types of sound-recording devices, such as the disk recorders, open a valuable new medium for professional records.

Aside from his surgical skill, the physician's greatest commodity in trade is his intellectual ability to interpret and to correlate. This is not impaired by the loss of one sensory modality.

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AMINO ACID COMPOSITION OF THE LENS PROTEINS OF THE BOVINE EYE

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ACCORDING to the monograph of Krause [1], Berzelius, in 1830, found 36 per cent protein in the lens of the bovine eye. He called it crystallin and stated that it was related to globulin. Mörner,[2] at the end of the nineteenth century, attempted the division and isolation of the various proteins of the crystalline lens, which yielded fractions having individual characteristics. Besides the insoluble protein, albuminoid, he obtained two water-soluble proteins, which he designated as α and β crystallins, and a fourth protein obtained in amounts too small for quantitative analysis. These fractions, in spite of the arbitrary conditions of separation, isolation and denomination, had a certain degree of individuality. They were subjected to elementary analysis, and their carbon, hydrogen, nitrogen and sulfur values were established.

Only after the advent of Emil Fischer's ester method did the investigation of the amino acid composition of the isolated proteins become possible. Jess [3] investigated the chemical composition of the lenticular proteins, following Mörner's methods of isolation of these proteins. He determined thirteen amino acids quantitatively in each of the three isolated proteins. Owing to the limitations of the available methods, the values he obtained can be given only a limited consideration. In these early investigations, at most 50 to 75 per cent of the amino acids present was recovered. Even such values, according to Abderhalden, were obtained only by highly skilled analysts.

Hijikata,[4] in his investigations, did not follow Jess's orientation. He did not isolate the individual proteins but, instead, hydrolyzed the whole

1. Krause, A. C.: Biochemistry of the Eye, Baltimore, Johns Hopkins Press, 1934.

2. Mörner, C. T.: Untersuchung der Proteïnsubstanzen in den lichtbrechenden Medien des Auges: I., Ztschr. f. physiol. Chem. **18**:61, 1894; II., ibid. **18**:213, 1894; III., ibid. **18**:233, 1894.

3. Jess, A.: Die moderne Eiweisschemie im Dienste der Starforschung, Arch. f. Ophth. **105**:428, 1921; Zur vergleichenden Chemie der Hornhaut und der Lederhaut des Auges, ibid. **112**:489, 1923.

4. Hijikata, Y.: On the Cleavage Products of the Crystalline Lens, J. Biol. Chem. **51**:155, 1922.

lens substance. His results varied widely from all others reported especially from those of recent investigators.

The continuation of Jess's research program, two decades later, by Krause,[5] brought a closer understanding of many problems and the possession of more exact data, and it laid the foundations of a knowledge which, supplementing morphology, made possible a biochemical approach to physiologic and pathologic processes.

Krause confirmed the presence of albuminoid, alpha and beta crystallins and albumin and showed the occurrence of a mucoprotein and a nucleoprotein in the crystalline lens. He emphasized that each of these lenticular proteins belongs to its respective class of proteins. He determined the nitrogen distribution of the individual proteins in the various layers of the lens tissue and showed their significant changes with advancing age. Using colorimetric methods, he determined the nitrogen distribution of six amino acids (cystine, arginine, histidine, lysine, tryptophan and tyrosine) in the albuminoid, in the alpha and beta crystallins, in the albumin and in the capsule of the lens.

To these data are added the results of Bloch and Salit [6] and, finally, those of Schaeffer and Shankman.[7] These investigators, like Hijikata, hydrolyzed the whole lens protein, and thus their values are not directly comparable with those of Jess and Krause. Bloch and Salit used chemical methods for the estimation of tyrosine, tryptophan, phenylalanine, cystine and methionine and the microbiologic assay method for lysine, leucine, isoleucine and valine. Schaeffer and Shankman estimated fourteen amino acids, all by the microbiologic assay method, after hydrolysis of the total lens proteins. Their data, therefore, are best comparable with those of Hijikata and of Bloch and Salit.

Investigations of the composition of the lens proteins may be divided into two groups: those concerned with the whole lens substance and those concerned with the composition of the separated lens proteins. The present investigation contributes to both groups.

METHODS [7a]

Separation of Proteins of the Bovine Lens.—The technic used was essentially that applied by Krause.[5] Briefly, the following steps were carried out: Fresh

5. Krause, A. C.: Chemistry of the Lens: I. Composition of Albuminoid and Alpha Crystallin, Arch. Ophth. **8**:166 (Aug.) 1932; II. Composition of Beta Crystallin, Albumin (Gamma Crystallin) and Capsule, ibid. **9**:617 (April) 1933; III. Autolysis of the Lenticular Proteins, ibid. **10**:631 (Nov.) 1933; IV. Am. J. Ophth. **17**:502 (June) 1934.

6. Bloch, R., and Salit, P. W.: A Note on the Amino Acids of Cataractous and Sclerosed Human Lenses, Arch. Biochem. **10**:277, 1945.

7. Schaeffer, A. J., and Shankman, S.: Amino Acid Composition of Proteins of the Ocular Tissues, Am. J. Ophth., to be published.

7a. The H. M. Chemical Laboratories of Los Angeles permitted us the use of their facilities and rendered technical assistance.

lens (20.92 Gm., or 13 lenses, representing 8.37 Gm. of dry material) was macerated with 5 cc. of cold water per lens. The insoluble albuminoid was centrifuged off and washed with a small amount of cold water, alcohol and ether and dried in vacuum. The yield was 1.00 Gm. (11.93 per cent of the dry material).

The filtrate was clarified by filtration and was made to p_H 5.2 with 10 per cent acetic acid. The bulky precipitate was filtered off and dissolved in 250 cc. of 10 per cent acetic acid. The solution was clarified by centrifugation, and the alpha crystallin was reprecipitated by the addition of 0.2 normal sodium carbonate and adjusted to p_H 5.2. The precipitate was filtered, washed with alcohol and ether and dried in vacuum. The yield was 2.60 Gm. (31.1 per cent of the dry material).

The filtrate from the alpha crystallin was adjusted to p_H 7.2 by the addition of 0.2 normal sodium carbonate. The bulky precipitate was filtered off, and the filtrate was dialyzed in collodion sacs (20 by 200 mm.) against water at 0 C. for seven days. The precipitate was combined with that obtained on neutralization, and the total was dissolved in water and redialyzed. The final product was washed with alcohol and ether and dried in vacuum. The yield was 4.32 Gm. (51.5 per cent of the dry material).

The filtrates were combined and saturated with sodium chloride and clarified by centrifugation. Acetic acid was added to maximum precipitation. The precipitate was redissolved in water, clarified, saturated with sodium chloride and acidified. The product was centrifuged, washed with alcohol and ether and dried in vacuum. The yield was 0.12 Gm. (1.4 per cent of the dry material).

Hydrolysis and Preparation of the Samples.—The samples were hydrolyzed in 13 by 100 mm. sealed pyrex® tubes with 1 ml. of five times normal solution of sodium hydroxide per hundred milligrams of sample (for tryptophan) and with 1 ml. of eight times normal hydrochloric acid per hundred milligrams of sample (for the other amino acids) by autoclaving at 15 pounds (6.8 Kg.) for twenty-four hours.

After being autoclaved, the tubes of acid solution were broken into an amount of sodium hydroxide solution calculated (to facilitate salt compensation) to give a known and equal concentration of sodium chloride in all neutralized sample solutions. Similarly, the tubes of basic solution were broken under a calculated amount of hydrochloric acid. The sample solutions were then neutralized to p_H 6.8 and made to volume.

Since the amino acid concentrations of most of the proteins were unknown, a concentration of about 400 micrograms per milliliter of the protein was used for each assay solution.

Technic of Assay.—The following procedure is varied considerably in different laboratories, depending on the amount of sample and other materials available, the tubes and racks available and the preference of the worker. The entire procedure as given here is that which we have found most convenient.

The samples are usually run at 7 levels in duplicate, and the standards at 15 levels in triplicate. A 3 ml. volume is generally used when sufficient sample is available, and the assays are carried out in 13 by 100 mm. test tubes held in rigid aluminum racks of 15 by 24 rows. Thus, 2 vertical rows of 15 tubes each will accommodate 3 samples of 5 levels in duplicate, or 2 samples of 7 levels in duplicate, with an empty space in the center dividing the samples. Each vertical row of 15 tubes will accommodate a replicate set of standards.

Into each tube is placed the desired amount of sample solution (or standard), the desired amount of medium and 1 per cent sodium chloride solution (or the same concentration of sodium chloride as the sample).

The sample solutions, standards, mediums and sodium chloride solution are transferred to the tubes with the aid of an automatic pipet, which is set to deliver 0.3 ml. aliquots. A solution of sodium chloride of the same concentration (in terms of sodium chloride) as the samples and standard is used in order to effect salt compensation. The organisms used are sensitive to variations in salt concentrations at low levels. Therefore the solutions are adjusted so that the sodium chloride concentrations are exactly the same in all the tubes. A concentration of about 1 per cent is optimum.

After all solutions have been added to the tubes, the racks are covered with several layers of toweling and are autoclaved at 15 pounds for ten minutes. The racks are then cooled to room temperature and are inoculated by aseptic addition of 0.1 ml. of inoculum suspension[8] to each tube with the automatic pipet. The pipet is sterilized beforehand by autoclaving the entire head and syringe assembly for ten minutes.

After inoculation the tubes are again covered with the toweling, which has been carefully kept from contamination, and are placed in the incubator at a temperature of 35 C. At the end of the period of incubation the tubes are sterilized by steaming ten minutes at 100 C., and they may be kept in the refrigerator until titrated.

The extent of growth in the tubes may be determined either by turbidimetry or by titration of the acid produced by the organisms. The tubes are titrated with dilute sodium hydroxide solution (0.01 normal per milliliter of volume; i. e., for a 3 ml. volume, 0.03 normal sodium hydroxide is used). The end point may be determined either by use of a p_H meter or with bromthymol blue (dibromthymol sulfonphthalein; 0.8 per cent in 50 per cent ethyl alcohol).

For titration with bromthymol blue, the content of each tube is washed into a small Erlenmeyer flask, a drop of the indicator is added and the solution is titrated with a dilute solution of sodium hydroxide to a prestandardized blue shade of the indicator.

For the so-called standard curve, the standard titrations are plotted against the number of micrograms of amino acid present per tube. The curve is carefully drawn, and the sample titrations are interpreted directly from the graph in terms of micrograms of amino acid per tube.

RESULTS

In the present investigation, bovine crystalline lenses from slaughter houses were used. Age variations were disregarded, although age

8. Stab cultures of Lactobacillus casei, Leuconostoc mesenterioides and Lactobacillus arabinosus are carried on yeast-dextrose agar (Difco) and Lactobacillus fermenti is carried on tomato juice agar (Difco). Cultures are transferred at two week intervals.

For preparation of the inoculum suspension a fresh twenty-four hour culture is used. A suitable volume of sterile inoculum medium is inoculated from the twenty-four-hour culture and is incubated twenty-four hours at 35 C., most conveniently in 15 ml. centrifuge tubes. The cotton plug of the tube is fastened with a rubber band to prevent its being thrown to the bottom of the tube, and the tube is centrifuged. The supernatant fluid is poured off, and the cells are stirred into a few milliliters of sterile saline solution. This suspension is then added to the desired volume of sterile saline solution for use as the inoculum suspension.

In some cases, in which particularly low blank titrations are desired, the cells are washed once with sterile saline solution before the final suspension in sterile saline solution.

variations of animals slaughtered for the packing industry are restricted, since the extremes of age are not as a rule represented in food for human consumption. Amino acid determinations on whole proteins of the crystalline lens of steer and calf by Schaeffer and Shankman [7] showed clearly that variations in the chemistry within these limited age categories are relatively small, often within the limit of experimental error. Really senile bovine lenses, possibly with cataract formation, are not easily procured from slaughter houses, since cattle are not often allowed to reach the age of senility. The problem of the distribution of the various proteins according to lamellar fractions was disregarded in the present investigation. The crystalline lens as a whole was examined. Only the four main proteins were isolated and analyzed; mucoprotein and nucleoprotein, two protein fractions the investigation of which is planned for the near future, were disregarded.

Table 1 shows the distribution of the four protein fractions examined in bovine lenses, as compared with the values found by Mörner [2] and by Krause.[8] A statistical evaluation of the accuracy of the amino acid values is given in table 2.

Table 3 is a comparative tabulation of the results of investigations made on the undivided whole proteins after hydrolysis of the entire lens tissue. It presents the results of the investigations of Hijikata,[6] Bloch and Salit [5] and Schaeffer and Shankman [7] and of the present study.

Besides the close harmony between the findings of the present investigation and those of Schaeffer and Shankman, the table points out clearly a great similarity of both these results to those of Bloch and Salit. Slight quantitative differences for tryptophan require further study and verification. The crystalline lenses compared were derived from different subjects. Human lenses are comparable with animal lenses only with reservation, not merely because of species differences but also because the examined human lenses usually showed opacities of various degrees.

Table 4 shows the relative distribution of amino acids in the four individual proteins of the bovine crystalline lens, according to all available information, including our own results. The nitrogen distribution is such as to verify the conclusion that each of the four proteins possesses chemical individuality. One is also tempted to conclude that beta crystallin is closely related to albumin and alpha crystallin to albuminoid. Within these protein pairs there are, of course, considerable differences, and it is likely that just these quantitative variations are the determining factors in the makeup, i.e., characterization, of the individual proteins. Examples of greater variations may be mentioned: The albumin of the lens contains 5.8 per cent threonine; beta crystallin, only 3.2 per cent. The similarity between alpha crystalline and albuminoid is not less conspicuous, although in these proteins the amino acid distribution is

TABLE 1.—*Distribution of Proteins in the Bovine Crystalline Lens According to Three Investigations*

Proteins	Distribution, %		
	Mörner	Krause	Schaeffer and Murray
Albuminoid	48.0	12.50	11.9
Alpha crystallin	19.8	31.74	31.1
Beta crystallin	31.4	52.30	51.5
Albumin	0.6	1.46	1.4

TABLE 2.—*Amino Acids of the Proteins of the Bovine Lens, Including a Statistical Estimation of the Accuracy of the Results*

Amino Acids, %	Albuminoid	Alpha Crystallin	Beta Crystallin	Albumin	Total Lens
Arginine	10.8	10.6	11.2	11.6	10.6
No. of values *	4	4	3	4	3
MDM *	4.9	1.4	1.0	2.4	1.3
Histidine	2.9	3.7	4.5	3.9	4.0
Values	4	3	4	4	3
MDM	3.6	3.7	2.1	10	2.6
Tyrosine	4.7	5.4	5.2	6.1	6.3
Values	2	2	1	4	2
MDM	4.8	2.3	....	6.0	0.4
Threonine	0.0	4.4	3.2	5.5	4.2
Values	3	6	3	3	3
MDM	4.4	9.6	4.5	7.8	6.5
Phenylalanine	9.5	10.6	6.9	4.8	8.0
Values	4	3	3	4	3
MDM	6.9	5.5	2.5	7.2	2.9
Lysine	5.7	4.8	5.1	4.0	5.2
Values	2	3	3	3	3
MDM	0.7	2.1	2.7	10	3.1
Glutamic acid	8.0	11.4	13.0	11.5	10.9
Values	3	3	3	2	2
MDM	2.7	2.5	1.3	1.2	4.9
Leucine	8.5	7.7	6.7	7.0	7.2
Values	4	3	3	3	3
MDM	1.7	4.3	2.4	7.0	0.2
Isoleucine	6.2	5.9	4.7	4.8	5.6
Values	4	3	3	4	3
MDM	2.2	1.2	2.7	2.5	0.9
Methionine	1.8	1.6	2.5	4.0	2.2
Values	5	3	3	4	2
MDM	0.5	2.6	4.2	6.6	2.0
Cystine	0.7	1.4	1.8	2.1	1.6
Values	5	4	2	4	2
MDM	3.0	4.6	11.5	5.5	12.0
Aspartic acid	6.3	7.5	8.6	10.2	7.8
Values	3	2	3	4	2
MDM	2.5	4.4	1.3	4.2	1.0
Valine	6.0	5.2	4.4	2.7	5.0
Values	3	2	2	5	3
MDM	4.0	7.8	2.0	4.1	6.9
Tryptophan	2.4	2.5	1.8	1.6	2.2
Values	3	4	3	4	3
MDM	2.7	2.2	4.6	2.2	3.9

* The number of replicate values obtained for each protein and the mean deviation from the mean of these values.

TABLE 3.—*Comparative Tabulation of Amino Acid Values for Total Undivided Proteins in Different Mammalian Crystalline Lenses According to Various Investigators*

Amino Acids, %	Hijikata	Bloch and Saltt	Schaeffer and Shankman	Present Investigation
Glycine	0	.....	4.5- 5.9	...
Arginine	2.3	.....	10.4-11.9	10.6
Histidine	1.6	.....	3.5- 4.9	4.0
Tyrosine	4.5	6.0	6.4- 7.9	6.5
Threonine	...	.....	3.5- 4.8	4.2
Phenylalanine	1.9	8.5-8.6	7.8- 9.2	8.0
Lysine	1.6	6.0	5.1- 6.0	5.9
Glutamic acid	15.5	.....	13.7-16.8	12.0
Leucine	6.6	7.2-7.5	7.8- 9.6	7.2
Isoleucine		6.2	5.2- 6.9	5.6
Methionine	...	3.5-3.8	2.3- 3.2	2.2
Cystine	...	1.5	.....	1.6
Aspartic acid	1.4	.....	.....	7.8
Valine	1.0	5.2	5.1- 6.1	5.0
Tryptophan	1.6	2.5-2.4	.....	2.2
Alanine	4.7	.....	.....	...
Proline	2.2	.....	.....	...
Serine	...	.....	6.0- 8.4	...

TABLE 4.—*Comparative Tabulation of Amino Acid Values for Individual Proteins of Mammalian Crystalline Lenses* According to Various Investigations**

Amino Acids, %	Albuminoid			Alpha Crystallin			Beta Crystallin			Albumin	
	1	2	3	1	2	3	1	2	3	2	3
Arginine	10.98	9.91	10.8	8.0	11.24	10.6	7.45	11.44	11.2	12.8	11.6
Histidine	3.73	3.3	3.9	3.81	3.65	3.7	3.59	4.28	4.5	3.32	3.2
Tyrosine	5.6	6.25	4.7	3.5	5.31	5.4	3.7	5.47	8.3	4.19	6.1
Threonine	...	.....	6.0	...	.....	4.4	...	.....	3.2	.....	5.8
Phenylalanine	4.6	.....	9.5	5.5	.....	10.6	1.4	.....	6.0	.....	4.8
Lysine	2.87	5.66	5.7	3.88	1.87	4.9	4.6	4.6	5.1	5.3	4.0
Glutamic acid	4.6	.....	9.0	3.6	.....	11.4	2.7	.....	13.0	.....	11.5
Leucine			8.3			7.7			6.7	.....	7.0
Isoleucine	5.5	.....	6.2	5.7	.....	5.8	2.8	.....	4.7	.....	4.8
Methionine	...	.....	1.8	...	.....	1.6	...	.....	2.5	.....	4.0
Cystine	3.1	1.25	0.7	2.3	1.11	1.4	4.9	3.18	1.8	3.58	2.1
Aspartic acid	0.5	.....	6.3	1.2	.....	7.5	0.4	.....	8.6	.....	10.2
Valine	0.2	.....	6.0	0.9	.....	5.3	2.1	.....	4.4	.....	3.7
Tryptophan	...	0.71	2.4	...	0.85	2.45	...	1.57	1.8	0.88	1.6
Alanine	0.8	.....	...	3.6	.....	...	2.8	.....	...	.....	...
Proline	1.9	.....	...	1.8	.....	...	3.7	.....	...	.....	...
Serine	...	.....	...	...	.....	...	...	.....	...	.....	...
		9			6			4		4	
Amino acetic acid		5.2±			5.2±			5.2±		5.3±	
Serine		7.9±			7.9±			7.2±		7.9±	
Hydroxyproline, Citrulline	No information available										

* 1 indicates Jess's values; 2, Krause's; 3, the present findings, and 4, average values of Schaeffer and Shankman for the undivided lens proteins.

characteristic enough. A greater discrepancy is seen for glutamic acid, of which the alpha crystallin contains much more than the albuminoid.

With respect to the real chemical relationship of these proteins to other, already better defined, simple proteins, it can be said only that such a relationship is definitely vague. A comparison of the values obtained for the first protein pair, beta crystallin and albumin, with the values obtained by other investigators for serum albumin, is disappointing. Such a hypothetic relationship is arbitrary and indefinite.

Our data compare favorably with those of Krause. The agreement between Krause's results and ours, especially for lysine, histidine and arginine, is rather close, though in another instance, that for tyrosine and cystine, the divergence is appreciable. Only further research will eliminate such differences, and it is to be hoped that data obtained with independent analytic methods will be available to clarify the as yet existing contradictions.

COMMENT

Jess found, as did Hijikata, that aminoacetic acid was completely missing from all proteins of the lens. On the other hand, in the investigation of Schaeffer and Shankman on the total proteins of the lens, aminoacetic acid was found to the extent of about 5.2 per cent. These contradictory findings may be explained by the low values for this amino acid in investigations by early colorimetric or Fischer ester methods. How this 5.2 per cent aminoacetic acid in the total proteins is to be theoretically distributed among the individual proteins cannot be predicted, and only further experimentation will give an adequate answer.

No definite opinion can be formed as yet concerning a few other amino acids. Of tryptophan, for example, Jess found only traces, whereas in the investigation of Krause its value was estimated to be approximately 1 per cent. The present findings are somewhat higher, being 2.4, 2.45, 1.8 and 1.6 per cent, respectively. These values are closer to the previous results of Schaeffer and Shankman, who determined for the total proteins an average value of 1.7 per cent. The values obtained earlier by Lieben and Kronfeld,[9] Süllman[10] and Bloch and Salit[6] are still higher. In an investigation of the etiology of tryptophan deficiency cataract in rats, we have previously estimated the tryptophan content of the crystalline lenses of animals fed normal diets and of rats fed a tryptophan-free diet.[11] In these experiments, the tryptophan

9. Lieben, F., and Kronfeld, P.: Ueber die Wirkung der Belichtung auf die Eiweisskörper der Augenlinse, Biochem. Ztschr. **197**:136, 1928.

10. Süllman, H.: Biochemie des Auges, Ophthalmologica, **113**:1, 1947.

11. Schaeffer, A. J., and Murray, J. D.: Tryptophan Determination in Cataracts Due to Deficiency or Delayed Supplementation of Tryptophan, Arch. Ophth. **43**:202 (Feb.) 1950.

contents of the normal lens and of the lenses with tryptophan deficiency cataract were found to be nearly the same, about 2.8 per cent. It seems likely that the tryptophan content of the crystalline lens varies according to species and other undetermined factors. Values for proline and alanine can be furnished only from the data of Jess and Hijikata.

Knowledge of the amino acid composition of the proteins of the lens, though still incomplete, offers a basis for biochemical research. The importance of such basic information is obvious. The accepted theory that proteins are composed of amino acids and that these building stones of the protein molecule are in a characteristic intermolecular arrangement, forming, in a higher organization, the tissue proteins of various composition, lends interest to the investigation of different problems of the physiology and pathology of the lens.

SUMMARY

The amino acid composition of both the total undivided proteins and the divided individual proteins of the crystalline lens of bovine eyes was estimated by the microbiologic assay method.

The data obtained are tabulated and compared with those of earlier investigators. A close harmony with the results of recent investigators appears.

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CLEARING EFFECT OF TRANSPLANTED CORNEA ON THE OPACITY OF THE RECIPIENT CORNEA

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IT HAS been observed clinically since the early experiences with corneal homotransplants that a successful graft is occasionally followed by a dramatic clearing of the nebulous cornea of the recipient surrounding the graft. This phenomenon has been commented on by von Hippel,[1] Sellerbeck,[2] Elschnig,[3] Kopp,[4] Filatov,[5] Welter,[6] and Imre,[7] among others. Imre pointed out that this clearing of the cornea around a transplant is most apt to occur in cases of interstitial keratitis and presented this fact as evidence that the opacity of the cornea in syphilitic interstitial keratitis is due not to scarring but to "colloidal-chemical" changes in the corneal stroma.

Filatov [8] suggested the possibility that transplants of cornea outside the pupillary area might influence the clearing of a central opacity in the pupillary area. This report emphasized the use of paracentral penetrating transplants in cases of dense leukoma in order to improve the central area before a central penetrating transplant was performed. It also recommended the use of paracentral lamellar grafts to improve the transparency of a central transplant which had become nebulous. Filatov devoted a great deal of attention to the clearing of corneal

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7. Imre, J.: Klinische und histologische Erfahrungen mit der Hornhautübertragung, Klin. Monatsbl. f. Augenh., Beihft 1942, pp. 1-50.

8. Filatov, V. P.: From Optical Corneal Transplantation to Therapeutic Tissue Transplantation, Arkh. Biol. Nauk. **50**:21-35, 1938; Healing of Keratitides and Other Diseases of the Cornea Through Tissue Transplantation, Vestnik oftal. **11**:295-310, 1937; Optical Keratoplasty and Therapeutic Transplantation of Tissues, Acta med. U. R. S. S. **1**:412-439, 1938.

leukomas after keratoplasty, and, on the basis of his observations, he ascribed a therapeutic, as well as a clearing, effect to corneal homotransplants. He elaborated a theory that the healthy corneal cells produce a substance which maintains the transparency of this tissue. However, when the normal cells are destroyed and healing occurs by the replacement of these cells, the new cells are no longer capable of producing the substance which maintains transparency, and clouding results. If a corneal graft remains clear in an opaque recipient cornea, the normal donor cell products diffuse into the adjacent cloudy cornea and lead to clearing. He also investigated this restorative effect in eyes with various inflammations of the cornea and reported favorable effects from lamellar grafts of cadaver cornea during the active states of tuberculous keratitis, herpetic keratitis and parenchymatous keratitis and in trachomatous pannus.

Welter [9] reported in detail on 3 cases in which "secondary" transplantations were performed in order to stimulate clearing of nebulous central grafts implanted, respectively, eleven months, one year and three years earlier. These "secondary" grafts, 2 of which were lamellar and 1 penetrating, were placed in juxtaposition to cloudy central grafts. In each case he reported clearing of the original transplant.

This early work of Filatov and his co-workers is particularly worthy of attention at present, since recent investigators [10] have once again reported therapeutic effects of lamellar homotransplants in cases of active keratitis. It is not within the province of this report to evaluate these possible therapeutic influences of corneal grafts. The "therapeutic effect," which has been investigated in relatively few cases, is mentioned here only to differentiate it from the "clearing effect," which has been observed by many surgeons and is well substantiated. Two such instances of clearing of the recipient cornea in cases of Groenouw's dystrophy were described recently by Paton.[10a] Castroviejo [11] observed some clearing of the surrounding cornea in every case of successful corneal transplantation. I have seen a pronounced clearing of the recipient's cornea around the graft following successful transplantation in cases of syphilitic interstitial keratitis, Groenouw's dystrophy, phlyctenular keratitis and disciform keratitis of long duration.

The apparent fact that in certain cases of corneal transplantation the donor tissue exerts a beneficial effect on the recipient cornea seems to be

9. Welter, S. L.: Clearing Up of Opacity of Transplant by Means of a Second Transplantation of the Cornea, Vestnik oftal. **10**:643-647, 1937.

10. (*a*) Paton, R. T., in discussion on Lamellar Corneal Grafts, in International Symposium on Corneal Surgery, Manhattan Eye, Ear and Throat Hospital, April 19, 1949. (*b*) Paufique, L.: Plaidoyer pour la greffe cornéenne non perforante, Ann. d'ocul. **180**:587, 1947.

11. Castroviejo, R.: Personal communication to the author.

a direct contradiction to the currently accepted belief that the important factor in transplantation is the state of the recipient cornea and that the donor tissue plays a rather passive role. Recent histopathologic studies tend to support the theory that the cells of the donor do not partake actively in regeneration. Messier and Hoffman,[12] on the basis of experimental corneal grafts with frozen donor material, concluded "that the cells in the donor cornea have no part in the healing of a corneal graft; rather, healing is the function of the cells of the recipient cornea. The maintenance of transparency of the graft appears to depend on the rapid passage of the recipient cells into the donor tissue when devitalized donor material is used."

Maumenee and Kornblueth,[13] in similar investigations with frozen tissue, were somewhat less certain that only the recipient cornea was concerned in the transparent healing of a corneal graft. They concluded that viable stromal cells were necessary in the graft, at least during the first stages of healing, but that the cells of the donor graft could be completely destroyed by freezing as early as eleven days after the transplantation without disturbing the transparency once the edema due to the injury had subsided.

EXPERIMENTAL STUDIES

The experiments to be described were undertaken several years ago and represent an attempt to study the "clearing effect" of corneal transplantation through another approach. In these experiments, in contrast to the methods previously described, the recipient cornea was injured and the donor cornea was implanted in a relatively normal state. The purpose was, first, to evaluate, if possible, the effect of implantation of such normal cornea in or about the damaged cornea and, second, to attempt to reproduce the "clearing effect" around the corneal grafts, as observed in human subjects.

Experimental Method.—Permanent corneal opacities were produced in a group of rabbits in the following manner: The animal was anesthetized with sodium pentobarbital, and topical anesthesia was produced with 0.5 per cent tetracaine hydrochloride. The pupil was dilated widely with atropine. A tightly rolled cotton applicator was saturated with 75 per cent hydrochloric acid, any excess being removed by touching the applicator to the glass stopper. The acid-soaked applicator was placed over the center of the cornea with light pressure so that approximately one half of the cornea was covered, and the applicator was kept in place for ten seconds. Great care was taken to avoid any spilling of the acid over the limbus and conjunctiva. Immediately on removal of the applicator, the eye was flushed with 5 per cent solution of sodium bicarbonate. Bubbles of gas appeared on the

12. Messier, P. E., and Hoffman, R. S.: Mechanism of Corneal Graft Healing: II. Behavior of Recipient and Donor Cells, Arch. Ophth. **42**:148 (Aug.) 1949.

13. Maumenee, A. E., and Kornblueth, W.: Symposium: Corneal Transplantation: IV. Physiopathology, Am. J. Ophth. **31**:1384, 1948.

corneal surface, and at this point the animal often struggled and made attempts to brush the eye, suggesting that the neutralization of the acid was accompanied with pain. A grayish white, fairly homogeneous opacity appeared immediately. An atropine ointment was placed in the cul-de-sac, and the eyelids were sutured. In the course of the next five days, the opacity increased in density and a few vessels entered the cornea. The height of the reaction occurred in about a week, and the vascularity then began to subside, followed by a slow decrease in the opacification. In the majority of the animals improvement came to a halt within four weeks. To make certain that subsequent changes were not spontaneous none of the animals were used for experiments before ten weeks had elapsed. Four animals, scarred in the aforementioned manner, were kept as controls for periods of five to six months. In none of these was any alteration in the leukoma observed later than eight weeks after the burn.

In one group, of 6 animals, clear lamellar corneal transplants, rectangular, 3 by 4 mm. in size and approximately two-thirds the corneal thickness, were placed in the recipient cornea so that one side of the graft lay from 1 to 2 mm. within the leukoma and the remaining margins lay within clear, or almost clear, corneal tissue. These rectangular grafts were used, rather than square or round grafts, for two reasons: First, it was desired to place as long a border of the transplant as possible in contiguity with the clear portion of the recipient cornea. Second,

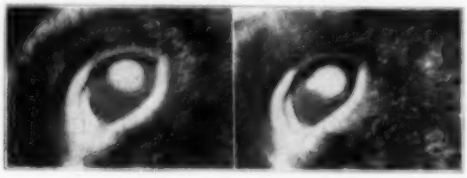

Fig. 1.—One of the control animals, showing the stationary character of the opacity. The photographs were taken at an interval of two months. No change was noted at the end of six months.

it was found that it was technically easier to resect a lamellar rectangle 3 by 4 mm. than a 4 mm. square. The grafts were taken from eyes which had been removed three to twelve hours previously and had been kept in a moist chamber at a temperature of 2 to 5 C. The rectangular grafts were outlined by means of the double-bladed knife of Castroviejo and were then dissected free from the underlying stroma with a Wheeler knife. The recipient cornea was prepared in the same way, except that a figure-of-eight suture of 000000 black silk was placed 0.5 to 1 mm. from the longer sides of the rectangle before the tissue was excised. This suture was tied over the graft to hold the latter firmly in position. Ointment containing 1 per cent atropine was placed over the cornea, and the lids were sutured with three interrupted black silk sutures. A gauze-collodion dressing was placed over the lids. All sutures were removed at the end of five days. Daily instillation of atropine was continued until the eye was free from any sign of congestion. The eye was observed for evidence of clearing of the corneal leukoma or of change in its size or shape over a period of two months, in the shortest case, and of six months, in the longest.

In a second group, of 4 animals, lamellar grafts 4 mm. square and two thirds of the thickness of the cornea were placed in the centers of the opacities so that all four sides were surrounded by the leukomatous or nebulous cornea. These

transplantations were made in the manner described in the preceding group except that the grafts were square instead of rectangular and they were held in position by two figure-of-eight sutures instead of one. The postoperative treatment and observation were as described for the preceding group.

A third group, of 6 animals, in which the cornea had been scarred as previously described, received penetrating transplants into the center of the corneal opacity. These penetrating transplants were placed by the technic of Castroviejo with minor modifications, as described by me elsewhere.[14] Two figure-of-eight sutures were

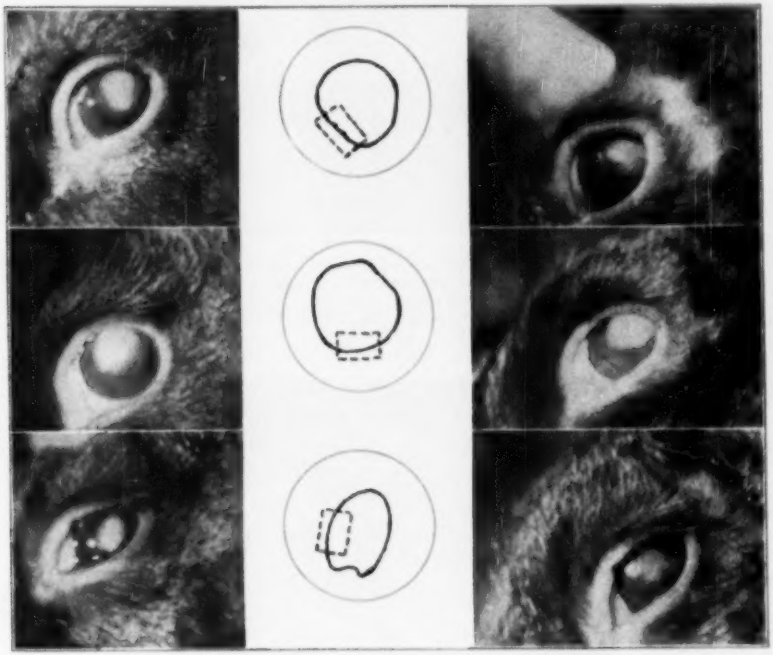

Fig. 2.—Lamellar corneal grafts in the margins of corneal opacities produced by hydrochloric acid. The diagrams indicate the positions in which the grafts were placed in each case. The postoperative photographs on the right show some change in the opacities at the sites of the transplants but no alteration elsewhere.

used for fixation. These were removed after seven days. The postoperative treatment was similar to that in the preceding group.

Results.—Lamellar Marginal Transplants: In the group of lamellar transplants placed at the margin of the corneal opacity, 3 of the trans-

14. Fine, M.: Homotransplantation of Preserved Cornea: An Experimental Study, Am. J. Ophth. **23**:1140, 1940.

plants were transparent and 3 were faintly nebulous. In none of these was there any change in the size or density of the opacity except where it was replaced by the transplant. Particular attention was devoted to

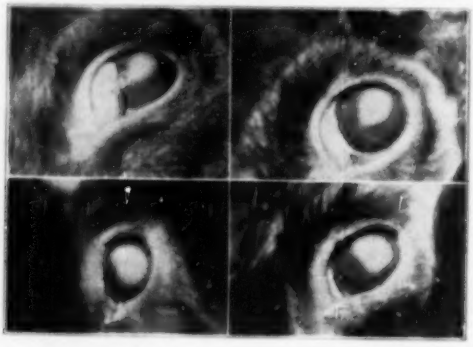

Fig. 3.—Lamellar grafts in the centers of corneal opacities produced by hydrochloric acid. The grafts have become opaque, and there has been no alteration in the size of the opacities. The postoperative photographs on the right show a slight clearing of the opacities in their centers, where the grafts were placed.

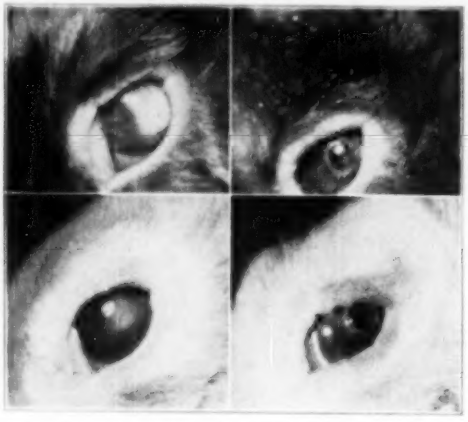

Fig. 4.—Partial penetrating transplants in opacities produced by hydrochloric acid. The postoperative photographs on the right show almost complete disappearance of the opacities about the grafts.

the opacity immediately adjacent to the transplant. In no case was there definite evidence of clearing about the graft (fig. 2).

Lamellar Central Transplants: In this group of lamellar grafts to the center of the opacified cornea, 1 was opaque, and 3 were nebulous. These are the results which were to be expected on the basis of past clinical and experimental experiences with transplants in badly scarred corneas. In none of them was there observed any clearing of the host cornea surrounding the transplant (fig. 3).

Penetrating Central Transplants: In this group of 6 animals in which penetrating transplants 4 mm. square were placed in the center of the corneal opacity, the results were extremely interesting and

Results of Transplantation of Cornea into Opacities Produced by Hydrochloric Acid

Rabbit	Type of Transplant	Length of Observation, Months	State of Transplant	Change in Recipient Cornea
C 1	Lamellar to margin *	9	Transparent	None
C 2	Lamellar to margin *	6	Faintly nebulous	None
C 3	Lamellar to margin *	3	Transparent over two thirds of area	Very narrow zone of partial clearing about 1 mm. wide, adjacent to line of union
C 4	Lamellar to margin *	6	Slightly nebulous	None
C 10	Lamellar to margin *	2	Transparent	None
E 4	Lamellar to margin *	2	Faintly nebulous	None
C 7	Lamellar to center *	2	Nebulous	None
C 9	Lamellar to center *	5	Nebulous	None
C 11	Lamellar to center *	2	Opaque	None
E 3	Lamellar to center *	2	Nebulous	None
C 5	Partial penetrating	3	Slightly nebulous	None
C 12	Partial penetrating	5	Faint nebula over one half; remainder transparent	Marked clearing of entire opacity, leaving only a faint nebula
C 17	Partial penetrating	5	Transparent, but slightly ectatic	Almost complete clearing of opacity
C 18	Partial penetrating	4	Transparent	Opacity reduced in size and less dense
C 19	Partial penetrating	2	Nebulous	Adjacent cornea clearer
E 2	Partial penetrating	2	Opaque	None

* The lamellar transplant was placed at the margin, or the center, of the opacity.

somewhat unexpected. Since the opacities were dense and involved all layers of the cornea, it was not anticipated that any transparent grafts would be obtained. However, 2 of the 6 experiments resulted in transparent grafts, although 1 was slightly ectatic and the other showed one nebulous corner. Of the remaining 4 transplants, 3 were nebulous and 1 was opaque. Both the animals in which clear grafts were obtained displayed marked clearing of the host cornea about the transplant, to the point where only a narrow ring of opacification remained about the line of union. In 2 of the 3 nebulous transplants there was a definite decrease in the size and density of the leukoma around them. In the third animal there was no appreciable change in the leukoma, as was the case with the animal in which the transplant became opaque.

COMMENT

To recapitulate, of 10 experiments in which successful lamellar homotransplants were placed in corneas with opacities following burn from hydrochloric acid, no clearing of the recipient cornea was observed elsewhere than at the site of direct replacement. On the other hand, of 6 experiments in which penetrating homotransplants of identical donor material were placed in similarly opacified corneas, definite clearing of the recipient cornea about the graft was noted in 4. These changes were not considered spontaneous, since control animals with similarly produced opacities exhibited no spontaneous clearing in the same period of time or longer.

The objection may be raised that the type of opacity produced in these experimental animals by hydrochloric acid was one in which clearing following transplantation was hardly to be expected, since such acid-burned corneas are notoriously poor ground for corneal transplants. Nevertheless, several clear, or almost clear, grafts were obtained in both the penetrating and the nonpenetrating groups of experiments.

In the transplants placed at margins of the opacities, about one half of the border of the graft was in contact with relatively healthy tissue. In these circumstances, it could be anticipated that some of the grafts might remain transparent. In this connection, Maumenee and Kornblueth found that grafts which were placed in cornea opacified with sodium hydroxide always became opaque if the opacity surrounded the graft but that some clear grafts could be obtained if the opacity was present on only one or two sides.

It is to be noted, also, that the opacities produced by the method described did not have the complications inherent in an uncontrolled, accidental acid burn of the cornea, in which the limbus and conjunctiva are usually involved as well as the central portion of the cornea. Such eyes usually have a secondary glaucoma. This complication is more detrimental to the ultimate clarity of the graft than is the nature of the scarring. Moreover, the experimental opacities described displayed limited vascularity, in contrast to accidental burns in which the cornea is usually heavily vascularized.

For the purpose of the experiments described, it appeared that a dense nebula or a light leukoma would be more desirable than a faint nebula, since small changes in transparency are more readily observable in the denser opacities. It is not proposed that the observations in these experiments in rabbits are translatable to similar opacities in the human cornea. The potential of the rabbit cornea for regeneration following various types of injury—mechanical, chemical and thermal—is much greater than that of the human cornea. This disconcerting fact has been apparent to many who have experimented with keratoplasty in the rabbit

and explains many of the discrepancies between the results of experiments in rabbits and clinical observations in man. However, it may be noted parenthetically that the type of case in which one might seek to utilize clinically an ameliorating lamellar or penetrating transplant would be one with a relatively dense opacity, such as was produced in these experiments.

CONCLUSIONS

Clearing of the recipient cornea around a corneal graft following a successful homotransplantation has been observed clinically.

An attempt was made to evaluate this phenomenon by a series of experiments in rabbits. In series of 6 and 4 successful lamellar transplantations to the centers and margins, respectively, of opacified corneas there was no clearing of the recipient cornea elsewhere than at the site of direct replacement. Of 6 animals in which partial penetrating transplants were performed with identical donor material to similarly opacified corneas, clearing of the recipient cornea around the graft was noted in 4.

The experiments suggest that the clearing of the recipient cornea observed after successful transplantations is due, at least in part, to circulatory and metabolic changes produced by the operation itself. On the other hand, the failure to observe any clearing after nonpenetrating transplantations suggests that the presence of the homologous tissue alone is not the complete stimulus for such clearing, although it may, indeed, play a minor part.

No statistical validity is claimed for these experiments.

COLOR PHOTOGRAPHY OF THE EYEGROUND

Report of an Improved Technic

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LOS ANGELES

THE FIRST to present in this country photographs of the eyeground taken with the improved Nordenson photographic ophthalmoscope was von der Heydt,[1] in 1926. Only a few years later, photography of the fundus in its natural colors was introduced by Wessely and Wertheimer.[2] Even though these early prints, taken with only two filters, were far from faultless, it was soon recognized that color photographs of the eyeground can be of great aid in the diagnosis of pathologic changes in the retina and choroid.[3] The technic of color photography of the fundus was greatly improved when films with three layers, using the three primary colors, became available[4] and it was no longer necessary to depend on coarse-grained plates and a set of filters.

While various types of equipment have been employed for color photography of the external eye,[5] as well as of the anterior segment,[6] it has never been seriously questioned that the Nordenson retinal camera is best suited to color photography of the eyeground.[7] However, the problem of how this instrument, which was originally equipped with a plate holder designed for black and white technic, can best be adapted to color photography has not yet been entirely solved. Bedell[8] attached

1. von der Heydt, R.: Photography of the Fundus, Tr. Am. Acad. Ophth., 1926, pp. 439-441.

2. Wessely, K., and Wertheimer, E.: Farbenphotographie des Augenhintergrundes, Klin. Wchnschr. **8**:1624 (Aug. 27) 1929.

3. Mann, W. A.: Color Photography of the Fundus Oculi: Description of New Method, Arch. Ophth. **8**:405-408 (Sept.) 1932.

4. Kugelberg, I.: Photographische Abbildung der Farben des Augenhintergrundes, Acta ophth. **10**:312-326, 1932.

5. Katzin, H. M.: Photography of the External Eye, Arch. Ophth. **35**: 514-518 (May) 1946.

6. Dekking, H. M.: Color Photography of the Eye, Arch. Ophth. **11**:225-228 (Feb.) 1934.

7. Koch, F. L. P.: Color Photography of the Human Ocular Fundus: Its Technic with the Zeiss-Nordenson Retinal Camera, J. Biol. Photog. A. **9**:119-135 (March) 1941.

8. Bedell, A. J.: Colour Photography in Ophthalmology, in Ridley, F., and Sorsby, A.: Modern Trends in Ophthalmology, New York, Paul B. Hoeber, Inc., 1940, pp. 213-223.

a film carrier of his own design to the standard plate holder. Bogart[9] mentioned "a special roll film adapter" by means of which he was able to use regular Kodachrome,* or Kodachrome films of Bantam* type in the Zeiss-Nordenson camera. No further technical details are given by either of these authors, but they apparently designed their own film carriers or had to rely on the Rollex* adapter. According to Koch and Williams,[10] the first procedure is likely to be comparatively expensive, while the film strip in the Rollex adapter is apt to tear easily; therefore they introduced certain modifications which made the adapter sturdier and, at the same time, easier to handle.

Many years ago, I began to experiment independently along different lines. Following a suggestion by representatives of the firm of Zeiss, I stripped a Kodak* Bantam camera of its bellows, lens and shutter and attached the bare frame to the Nordenson ophthalmoscope, so as to serve as a holder for Kodachrome Film K 828 A. Color photographs of the eyeground taken with this equipment, however, proved to be far from perfect. By attaching the Bantam camera to the ophthalmoscope as a holder for color film packs, the plane of exposure is moved back at least 2.5 cm. as compared with the proper focal distance for plates or film packs used in black and white photography. The depth of focus, therefore, had to be calculated anew for each successive exposure, but even then it was impossible to obtain pictures of standard quality.

Another approach to the problem of color photography of the fundus proved more successful. It was reasoned that the metal film pack in which Kodak Super-XX Panchromatic Film is supplied, and which fits into the film pack holder of the Zeiss-Nordenson camera, might later, when empty, serve as a color film carrier. The empty metal film pack can easily be inserted into the Nordenson camera, but this technic became practicable only after Kodak Ektachrome* film had appeared on the market. The sheets of this multilayer color film come in various sizes, and when they are cut in the darkroom to the dimensions of the metal casing of the Kodak Super-XX Panchromatic Film ($1^{13}/_{16}$ by 3 inches) they can be fitted into the color film carrier. In my experience, it has proved most economical to use sheets measuring 4 by 5 inches, from which three segments with the required measurements may be cut. A supply of empty metal film packs, which will serve as color film carriers, can be procured from any camera dealer.

Initially, the segment of the Ektachrome sheet was inserted into the front portion of the metal film pack holder, just beneath the metal frame and in front of the back plate. After a number of trials, however, this

9. Bogart, D. W.: Kodacolor Fundus Prints: A New Technic, Arch. Ophth. **29**:278-281 (Feb.) 1943.

10. Koch, F. L. P., and Williams, A. F.: A Modified Film Adapter for Retinal Photography, Am. J. Ophth. **27**:403-407 (April) 1944.

method proved disappointing. The back plate, resting on a spring, is pushed forward, together with the film, against the stable frame. However, the spring in the metal casing was calculated to last only for twelve exposures. Consequently, the automatic adjustment designed to insure accurate focusing by maintaining all films of the pack in the same vertical position failed after a number of additional exposures. In order to adapt the metal casing for permanent use as a color film carrier, it became necessary to design another device by which color film could be stabilized at the correct focal distance even during repeated exposures.

To this end, the metal back piece, together with the spring, and the top piece, intended to prevent penetration of light into the film pack, were removed. Only the bare outer frame of the metal film pack

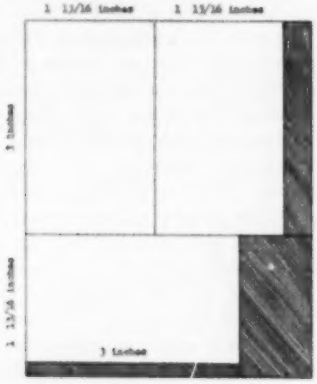


Fig. 1.—A sheet of Kodak Ektachrome film 4 by 5 inches divided into three equal portions, measuring $1\frac{13}{16}$ by 3 inches each. One-fourth reduction.

holder was retained, and a piece of wood was cut to fit precisely the inside measurements of the metal frame, care being taken, however, to leave just enough room between the front piece of the metal frame and the wooden block to accommodate one thickness of Ektachrome film. Finally, the top of the horizontal bar of the front piece of the film pack casing was removed, and it thus became possible to insert the Ektachrome segment without opening the casing.

In this simple and inexpensive manner a color film carrier is fashioned which will always prove completely reliable and, therefore, may be used for an unlimited number of exposures. As the spring has been replaced by a wooden block, the film is lodged in the same plane at every successive exposure. With the new film carrier, furthermore, color photographs of the eyeground by means of the Nordenson photo-

graphic ophthalmoscope are taken at the same focal distance as that used for black and white photographs, and clear pictures may thus be obtained without the need of special calculations.

Certain precautions are necessary, because the small metal cover which ordinarily protects the black and white film pack from penetrating

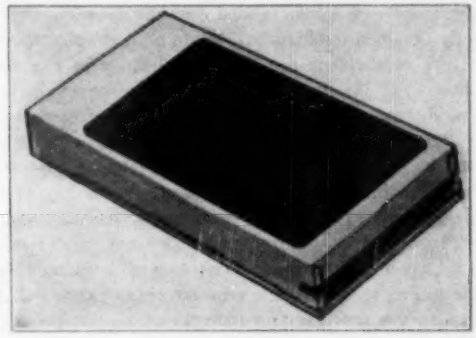


Fig. 2.—An empty metal film pack casing for Kodak Super-XX Panchromatic Film.

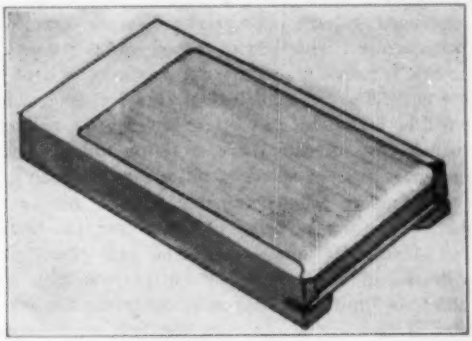


Fig. 3.—Back plate and spring, as well as the top of the horizontal bar of the front piece, are removed, and a wooden block is fashioned to fill the empty casing. A segment of Ektachrome film can then be inserted between the wooden block and the metal frame.

light rays has to be removed in order to adapt the metal frame to the use of color film. After it has been loaded, the color film carrier is therefore stored in an envelope of heavy black paper, which, in turn, is placed in a heavy black paper envelope of slightly larger size. Each

envelope is tightly secured with rubber bands. Once the color film adapter is placed in the Zeiss film pack holder, no further precaution is required, as the closely fitting wooden block constitutes in itself a considerable protection of the color film.

The sensitivity of Ektachrome film differs from that of any type of black and white film, as well as from that of other color films, and a much greater volume of light is needed. As the Zeiss-Nordenson camera was originally designed for black and white photography, the dimensions of the aperture of the lens are fitted exclusively to the requirements of that technic. For the purpose of color photography the smallness of aperture has, therefore, to be compensated by an increase in the time of exposure. By way of a first approximation, it may be stated that Ektachrome film should be exposed twice as long as any other type of film, or about the time it takes to count slowly to 5. These figures, however, are far from exact and are presented merely as rough directions for first experimentation. After trial and error, and with increased experience in the new technic, the operator will undoubtedly be able to adjust the timing to the specific requirements of each individual case. A longer exposure is necessary for patients whose pupils cannot be fully dilated and also for dark-skinned persons.

For use in the Nordenson photographic ophthalmoscope, Ektachrome Film Type A, designed for daylight color photography, is preferred. In initial experiments, Ektachrome Film Type B, designed for artificial light, was employed, but the photographs obtained were by no means completely satisfactory. The light of carbon arc lamps, as it is used in the Zeiss camera, is for all practical purposes the equivalent of daylight, and therefore color film for daylight exposure will lead to much better results. It will be found that in the transparency the red component is less accentuated, that all colors are more natural and, furthermore, that the differences in color values stand out more clearly.

The new method of color photography of the fundus of the eye, which has been tested for the better part of a year, can be said to have a number of striking advantages. In the first place, photographic stores will develop a single sheet of Ektachrome film, whereas the entire roll had to be finished as long as Kodachrome film was employed. Thus, no time is now lost in obtaining the finished transparency, and the practical importance of color photography of the eyeground for the diagnosis of diseases of the fundus is considerably increased. Loading of the Zeiss film pack holder is much simpler and proceeds faster than in any one of the older methods of color photography.

As long as the Kodak Bantam camera was used as an adapter for color film, it was difficult to present the eyeground in its entirety in a single picture, and certain portions of the fundus were likely to be missing, especially at the top and at the bottom. With the new Ekta-

chrome technic, the resulting photograph is at least one third larger than that with the Bantam camera, and lesions of the fundus, whatever their dimensions, are completely visible.

Another advantage of fundus photography with Ektachrome film is that the color values in transparencies, as well as in prints, are much more accurate and distinctive than with other methods of color photography of the eyeground; thus, the finer structure of the fundus becomes fully apparent, and pathologic changes can be studied in every minute detail.

Ektachrome film is designed for reversal processing, and positive color transparencies will result. These can be mounted on slides or may be reproduced in color or in black and white prints.

SUMMARY

An improved technic of color photography of the eyeground by means of the Zeiss-Nordenson photographic ophthalmoscope is presented. The back piece and the spring are removed from the metal casing of a Kodak Super-XX Panchromatic Film pack holder and are replaced by a wooden block, which will keep a segment of the Kodak Ektachrome color sheet film firmly in place. This color film adapter is easily loaded into the Zeiss film pack holder, and the films are developed after exposure of three segments of an Ektachrome sheet. The resulting pictures show the fundus in its entirety and are of higher fidelity than any hitherto achieved with any other technic. Transparencies, as well as color prints, may be obtained.

Clinical Notes

A WINGED EYE SPECULUM

CONRAD BERENS, M.D.
NEW YORK

One of the hazards of intraocular surgery is the escape of vitreous due to pressure on the eyeball. When pressure on the eyeball is observed, it becomes necessary for the surgeon to resort to sutures or retractors

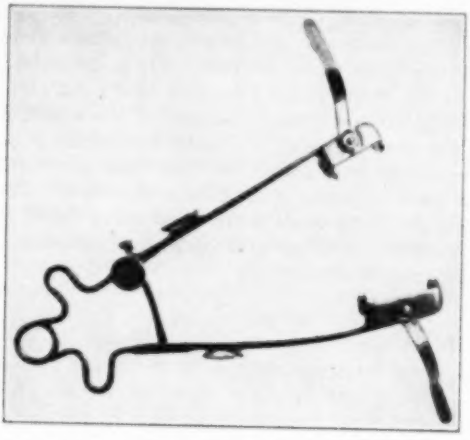


Fig. 1.—A winged eye speculum (Schmerl).

in order to control the eyelids. Retraction of the eyelids by sutures may not afford a sufficiently large operative field, particularly in operations for glaucoma or in cataract extraction, and in some instances the eyelids may still exert pressure on the eyeball. This pressure is frequently observed at the end of a time-consuming corneal transplantation.

The winged eye speculum relieves pressure on the eyeball and transfers pressure to the site where the wings rest on the bones of the face. This speculum is the outcome of Dr. Ernst Schmerl's courtesy in giving me his excellent speculum, which has two extensions (fig. 1). Two

The instrument is manufactured by E. B. Meyrowitz & Co., New York.

This study was aided by a grant from the Ophthalmological Foundation, Inc.

extensions with a lateral wing were merely added to the speculums for adults and infants previously described.[1]

Each of the three wings or extensions of the eye speculum for adults is 30 mm. in length and 4 mm. in width and may be bent to conform with the contour of the patient's face. At the extremity of each wing is a smooth raised knob which prevents discomfort from pressure on the tissues (fig. 2).

The eye speculum with solid blades is introduced between the eyelids in the usual manner, and the wings are adjusted to rest comfortably, but with some pressure, on the frontal and malar bones, above and below,

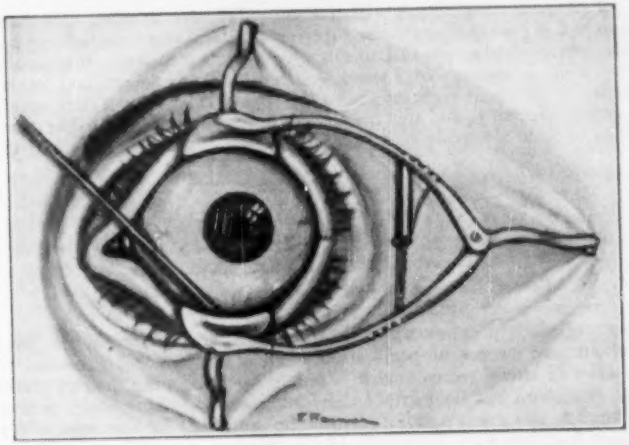


Fig. 2.—Winged speculum for adults (Berens). Two extensions and a lateral wing have been added to the solid blades of the speculum and the joint. The extensions are adjusted to relieve pressure on the eyeball. A spatula is used to exclude pressure on the eyeball.

and on the temporal muscle, laterally. Thus pressure is transferred to the facial bones and muscle, and the eyelids are widely retracted and held away from the eyeball. A spatula is passed between the blades of the speculum and the eyelids to make certain that there is no pressure on the eyeball.

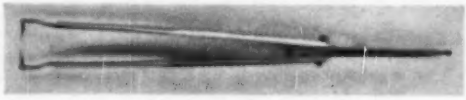
708 Park Avenue.

1. Berens, C.: An Eye Speculum, Tr. Sect. Ophth., A. M. A., 1932, pp. 357-358; An Eye Speculum for Infants, Tr. Am. Acad. Ophth. **44**:391-393. 1939.

NEW FORCEPS FOR GRASPING THE RECTUS MUSCLES

D. E. ROLF, M.D.
CLEVELAND

I presume that I have had the same difficulty at times that others have had in trying to grasp the superior or lateral rectus muscle. I have therefore devised a new instrument which seems to perform this function very well. It consists of a shank which is 4 cm. in length and has two blades at the tip at right angles to the shank. These blades are pressed together manually, and this maneuver causes the two needle-like extensions to slide alongside each other in a parallel manner. One can then



Forceps for grasping the lateral or superior rectus muscle.

exert as much pressure as necessary against the surface of the sclera without any danger of perforation. When the blades are closed, the superior or lateral rectus muscle is caught easily between the two needle-like extensions and held firmly. The inner surface of the blades is made somewhat concave to conform with the convexity of the sclera. The blades together with the needle-like extensions are 6.5 mm. in length and are made of stainless steel.

The following steps explain the method of grasping the rectus muscle:

1. The instrument is pressed down firmly against the sclera, forcing the horizontal blade against the surface of the sclera. The two blades are then pressed together, and the rectus muscle is caught between them as they slide past each other in a parallel direction.

2. Manual release permits the two blades to separate, and the grip on the muscle is loosened.

This instrument can be secured from V. Mueller & Co., Chicago.

A CAMERA FOR STEREOSCOPIC PHOTOGRAPHY OF THE ANTERIOR SEGMENT

DAVID D. DONALDSON, M.D.
BOSTON

IT GOES without saying that the primary objective of photography is to reproduce the actual conditions as exactly as possible. The stereoscopic photograph not only increases the impression of reality over that of the flat photograph but also often illustrates features which otherwise cannot be shown photographically. The various transparent media of the anterior segment offer multiple depths at which abnormalities can be visualized, and photography in the third dimension is required to demonstrate these locations. Furthermore, the effect of loss of detail due to the physical limitations of the film is appreciably reduced in the stereoscopic presentation (with the viewer or in stereoscopic projection), a fact which is explicable by the theory of replacement.[1] The purpose of the present communication is to describe a stereocamera having several features which have not previously been utilized in stereoscopic photography of the eye,[2] but which I have found advantageous. These features are (1) a wide range of focusing for variable magnification. (2) adjustment of the interlens distance for producing variable depth effects and (3) correction for parallax without producing distortion.

APPARATUS

The equipment (fig. 1) consists of two cameras facing each other and connected to their respective lenses by bellows. The lenses, in turn, face into a pair of right angle prisms, and the other surface of each prism faces the object being photographed. By means of a right and a left hand threaded screw, the prisms and their associated lenses (fig. 2) may be moved equally and in opposite directions. This variability of the interprismatic distance determines in effect the interlens distance. Since these prisms are only large enough to cover the area of the actual lens itself, it is possible to have the small interlens distance necessary for photographs in magnification. In addition, the entire prism lens assembly can be adjusted forward and backward to obtain the correct alinement for parallax. This is, in effect, the same as, but mechanically simpler than, moving the cameras forward and backward

1. Verhoeff, F. H.: A New Theory of Binocular Vision, Arch. Ophth. **13**: 151-175 (Feb.) 1935.

2. Drüner, L.: Ueber Mikrostereopsie und eine neue vergrössernde Stereoskopcamera, Ztschr. f. wissensch. Mikr. **17**:281-293, 1900. Metzger, E.: Augenartz und Photographie, Klin. Monatsbl. f. Augenh. **79**:1-17 (July) 1927. von der Heydt, R.: Stereophotography of the Anterior Eyeball and Fundus, J. A. M. A. **89**:1672-1673 (Nov. 12) 1927. Hughes, W. L.: Stereoscopic Photography as Applied to the Eye, Arch. Ophth. **3**:583-587 (May) 1930. Drüner, L.: Medizinische Kinemato-und Photographie über vergrössernde Stereoskopie, Deutsche med. Wchnschr. **59**:652-653 (April 28) 1933.

until identical fields are obtained in them. The two cameras (fig. 1) are movable toward and away from each other by means of another right and left hand threaded screw, and this makes possible various magnifications. Approximately 30 cm. of bellows extension on each camera can be obtained. The two cameras are parfocal, and thus only one is equipped with a ground-glass focusing attachment.

A pair of electromagnetic tripping devices (fig. 1) are attached to the shutter releases on the cameras and are wired in series to insure simultaneous shutter action; these are activated by a foot switch. The light source (fig. 1) is similar to the illuminants already described for ocular photography[3] and consists in an electronic flash tube (General Electric, FT 220) and cone. This source of light is attached to the stereocamera so that movements of one will be accompanied with a corresponding change in position of the other. Thus, the light source and camera are always alined with each other. Owing to the small size of the prisms, the cone of the illuminator may lie close to the optical axis. This results in almost direct-on illumination, thus producing uniform lighting and avoidance of lid shadows. With this arrangement, a lens aperture as small as f/18 may be utilized in taking a picture twice the actual size and on an emulsion having the speed of color film.

OPERATION

First, the magnification is selected which will best show the features to be photographed. Next, the adjustment of the interlens distance is made to obtain the proper stereoscopic effect at this magnification. Then, to obtain proper alinement for parallax correction, the prism-lens assembly is adjusted. The adjustment of this assembly depends on the magnification selected and the interlens distance being used and is indicated by calibrations on the track of the prism-lens assembly. The calibration scale for magnification is shown along the bellows extension track, and that for interlens distance is shown on the millimeter scale between the prisms. Only a certain number of the more commonly used combinations of interlens distance and magnification are calibrated on the scale of the prism lens assembly, but in most cases these suffice. However, if the operator wishes to utilize a different combination, he may obtain a proper correction for parallax by use of a small light source. A lens which can be swung into a position in front of and midway between the prisms (fig. 2) focuses the filament of the source on the subject. When the prism assembly is adjusted so that the focused image of the filament on the subject becomes centered in the ground glass, it will also be centered in the other camera, and identical fields will be obtained. Focusing of the image is then accomplished by means of a rack and pinion on which the stereocamera and light source are mounted. The picture is taken by the foot switch, which accomplishes three things: (1) It activates the electromagnets that trip the shutters; (2) it turns off the focusing lights mounted in the cone, and (3) after a momentary delay, it triggers the electronic flash tube. The flash of the lamp is timed to occur during the one-eighth second that the focal plane shutter is open.

COMMENT

Experience has shown that, even though the indicated focal lengths of the lenses are the same, they must be further matched to insure substantially the same image size. The ordinary miniature camera lens gives good results. However, the most satisfactory lens I have found

3. Trotter, R. R., and Grant, W. M.: Electronic Flash (Gas Discharge) Tube in Photography of the Anterior Segment of the Eye, Arch. Ophth. **40**:493-496 (Nov.) 1948.

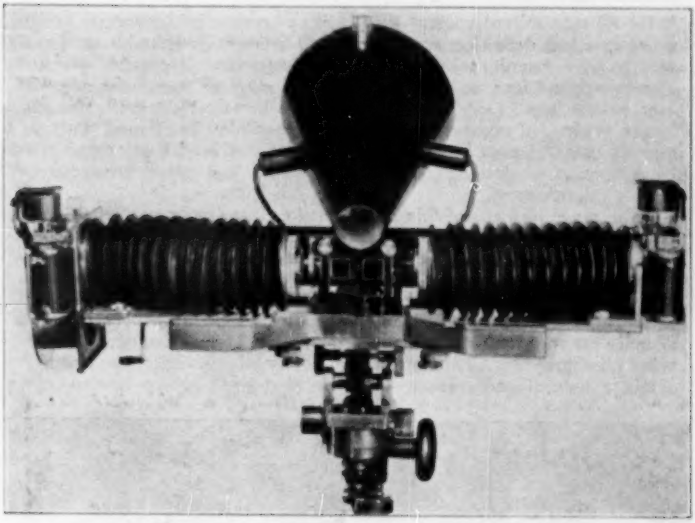


Fig. 1.—Front view of the stereocamera. The cone above the camera encloses the electronic flash tube at its base and the focusing lights at either side.

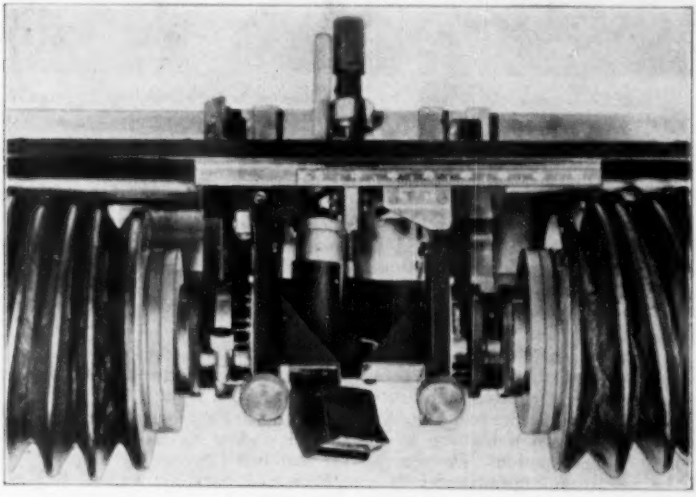


Fig. 2.—Top view of the prism-lens assembly after the cone has been removed. The special focusing attachment for parallax correction (see text) is swung into position in front of the prisms.

is the 80 mm. microsummar® lens (Leitz) because its symmetric design gives excellent definition at close range. When it is desirable or necessary to have magnification at distances greater than is possible with the aforementioned lens, as in photography of surgical operations, the 135 mm. hektor lens (Leitz) has been found to be suitable. With this lens larger prisms, of course, must replace the smaller ones used with the microsummar® lenses in order to cover the increased lens areas. The equipment is so designed that various lenses and prism sizes can be readily interchanged.

The range of focus of this camera makes it versatile enough to allow photographing of the entire face or limiting of the picture, for example, to a part of the cornea only. As a matter of fact, it has a range which permits continuous variable magnification up to seven times actual size, as well as focusing at infinity. The feature of the variable adjustment of the interlens distance makes possible the use of the proper interlens distance for the particular magnification and the type of subject which is being photographed. This adjustment is essential in order that one may obtain a natural and realistic effect or, if desired, a hyperstereoscopic

Fig. 3.—Stereoscopic pictures originally taken on kodachrome® film at magnification of 1½ actual size, showing tuberculous sclerokeratitis.

effect in the final photograph. Adjustment can be made to obtain an interlens distance ranging from 16 to 125 mm. The important feature of correction of parallax is obtained through translation, and not by the more conventional means of convergence on the object being photographed. The latter method produces the "keystoning," or wedge distortion, which is particularly objectionable in the close-up photograph. This stereocamera avoids such a distortion by the use of right angle prisms and by correcting for parallax through translation, thus effectively maintaining the image and object planes parallel.

Undoubtedly, this equipment has certain disadvantages and complications, some of which can be eliminated as improvements are incorporated. A desirable addition would be the use of a reflex housing to make possible the focusing of the image up to the moment the picture is taken. Such a housing to replace the sliding focus attachment is now in construction. Despite the fact that two cameras are employed, the operation approximates in simplicity photography with a single camera in that the two cameras are parfocal and parallax correction is quickly and easily accomplished.

SUMMARY

In photography of the anterior segment, depth relationships of abnormalities in the transparent media of the eye are best visualized in the stereoscopic color photograph. The stereocamera described has been found to be satisfactory in obtaining such photographs and incorporates features which have not previously been utilized in ocular photography and which permit the taking of a wide range of types of pictures. Some of these important features are wide range of focusing for variable magnification, adjustment of interlens distance for producing variable depth effects and correction for parallax without distortion. Although two cameras are utilized, the operation approaches the simplicity of a single camera.

Howe Laboratory of Ophthalmology.

Correspondence

AUREOMYCIN IN TREATMENT OF VIRUS DISEASES

To the Editor:—In the April issue of the ARCHIVES, under "Correspondence," there was published a letter on "Aureomycin in the Treatment of Virus Diseases," by George A. Sheehan Jr., M.D. Dr. Sheehan reported the local use of aureomycin in a case of "conjunctivitis of supposed Newcastle disease."

Aureomycin is undoubtedly a beneficial therapeutic agent in the treatment of virus diseases. However, in January 1950, I had under my care a proved case of Newcastle's conjunctivitis which occurred in a virologist. My associates and I were able to demonstrate inclusion bodies within the epithelial cells both before and after the administration of aureomycin drops, and we found that the drug in no way altered the course of the disease, the presence of which, I repeat, was verified in this case by virologic studies.

The inclusion bodies were demonstrable in scrapings, but not in smears, of the conjunctiva, and the disease was passed through chick embryos.

This case was reported before the College of Physicians of Philadelphia, Section on Ophthalmology, at the April 1950 meeting, by Dr. Arthur Keeney, of the Wills Eye Hospital, and Dr. M. C. Hunter. It will be published shortly as "Human Infection with Newcastle Virus of Fowls."

Wong and Cox, likewise, reported that aureomycin was without effect in experimentally infected animals (Wong, S. C., and Cox, H. R.: Action of Aureomycin Against Experimental Rickettsial and Viral Infections, *Ann. New York Acad. Sc.* **5**: 290 [Nov. 30] 1948).

2028 Pine Street (3). B. C. GETTES, M.D., Philadelphia.

CROSS CYLINDER TESTS

To the Editor:—Recently I attended an instruction hour at a meeting of the Section of Ophthalmology at the New York Academy of Medicine on cross cylinder tests, conducted by Dr. J. I. Pascal, and I have been wondering since why the technic as outlined at that lecture is not described in any of the current textbooks on refraction. Neither has it been taught me in any of the courses in refraction which I have taken. Dr. Pascal's technic consists in making all astigmatic tests while the eye is maintained in what he calls meridional balance, that is, with the retina straddling the interval of Sturm at the circle of least confusion. He explained the reasons for the superiority of this method over the usually taught technic of making the test while the eye is fogged fully or slightly.

I have since adopted Dr. Pascal's recommendations in my practice, with increased effectiveness. It would be well to have this method made known to other physicians. If they would try it, I believe, they would agree that it is the better technic.

DAVID I. MIROW, M.D., New York.

227 East Twentieth Street (3).

THE MOTAIS OPERATION

To the Editor:—Many years ago Shoemaker expressed the belief that any good result from a Motais operation is due merely to an adhesion of the tarsus to the globe. Spaeth believes this to be true and argues for the firmest possible attachment. Recently Berke (An Operation for Ptosis Utilizing the Superior Rectus Muscle, ARCH. OPHTH. **42**: 685 [Dec.] 1949) has described an operation which exactly carries out Spaeth's idea. His article is responsible for this letter.

For twenty-five years I have been performing the Motais operation by a technic that does not anchor the tarsus to the globe. This is proved in two ways: 1. On eversion of the lid the upper edge of the tarsus presents in a normal way. 2. In several cases there was enough downward deviation to require reoperation to cinch the untransplanted portion of the superior rectus muscle. In each case there was no trouble, and the tarsus did not enter the picture.

Should any one be interested, I shall be glad to send him an outline of the method.

RODERIC O'CONNOR, Oakland, Calif.

411 Thirtieth Street (9).

News and Notes

EDITED BY DR. W. L. BENEDICT

SOCIETY NEWS

Joint Meeting of North Carolina Eye, Ear, Nose and Throat Society and South Carolina Society of Ophthalmology and Otolaryngology.—There will be a joint three day meeting, on Sept. 11, 12 and 13, of the North Carolina Eye, Ear, Nose and Throat Society and the South Carolina Society of Ophthalmology and Otolaryngology. Headquarters will be the Skyland Hotel, Hendersonville, N. C.

The following otolaryngologists will be on the program: Dr. Fletcher D. Woodward, University of Virginia Department of Medicine, Charlottesville, Va.; Dr. Lester A. Brown, Emory University School of Medicine, Atlanta, Ga.; Dr. B. T. Horton, Mayo Clinic, Rochester, Minn., and Dr. Donald F. Proctor, Johns Hopkins University School of Medicine, Baltimore.

The following ophthalmologists will present papers:

Dr. Bruce Fralick, University of Michigan Medical School, Ann Arbor, Mich.; Dr. Edmund B. Spaeth, University of Pennsylvania School of Medicine, Philadelphia; Dr. Frank Walsh, Johns Hopkins University School of Medicine, Baltimore; Dr. Richard G. Scobee, Washington University School of Medicine, St. Louis.

Further information may be obtained from Dr. MacLean B. Leath, secretary, North Carolina Eye, Ear, Nose and Throat Society, High Point, N. C., or Dr. Roderick Macdonald, secretary, South Carolina Society of Ophthalmology and Otolaryngology, Rock Hill, S. C.

New York Eye and Ear Infirmary Alumni Association.—The first annual clinical meeting of the New York Eye and Ear Infirmary Alumni Association was held on May 11 and 12 at the New York Eye and Ear Infirmary. Among those participating in the program were Drs. Brittain F. Payne, William Y. Sayad, Fred W. Dixon, Joseph A. Sullivan, J. Calhoun McDougall, Joseph C. Ray, Elbyrne G. Gill, D. Harbert Anthony, John H. Sulzman, A. Russell Sherman, Jay G. Linn, William F. Ryan and Algernon B. Reese. In conjunction with this meeting, the section on ophthalmology and otolaryngology of the Medical Society of the State of New York met at the Statler Hotel on May 11 and May 12, respectively.

GENERAL NEWS

Walter R. Parker Lecture in Ophthalmology.—Dr. Kenneth C. Swan, professor of ophthalmology, University of Oregon Medical School, Portland, Ore., gave the first Walter R. Parker Lecture in Ophthalmology at the University of Michigan Medical School at the annual spring postgraduate course in ophthalmology on April 25. The subject of his lecture was "Some Contemporary Concepts of Scleral Disease."

Canadian National Institute for the Blind Fellowship in Ocular Genetics.—The University of Toronto Faculty of Medicine announces renewal of the Canadian National Institute for the Blind Fellowship in Ocular Genetics. The grant is $2,000 for research in this field. This fellowship was held during 1949-1950 by Dr. L. A. Probert, of Moose Jaw, Saskatchewan, Canada, who has been carrying on studies of the hereditary aspects of glaucoma. Dr. G. A. Thompson, of Richmond Hill, Ontario, Canada, has been appointed to continue these studies next year through funds provided by this fellowship.

PERSONAL NEWS

Dr. James H. Allen Appointed Professor of Ophthalmology at Tulane University.—Dr. James H. Allen, formerly professor of ophthalmology at the State University of Iowa College of Medicine, has been appointed professor of ophthalmology, Tulane University of Louisiana School of Medicine. Dr. Allen assumed his duties on March 1 and will be in charge of all ophthalmologic research projects, as well as the postgraduate courses in ophthalmology. Dr. William B. Clark will remain as chairman of the department and coordinator of all the affairs in the department. In addition to the expansion of the course in the basic sciences of ophthalmology which has been given by the department of ophthalmology of Tulane University for the past several years, several short courses for specialists in ophthalmology will be added to the postgraduate curriculum for next year.

Abstracts from Current Literature

EDITED BY DR. WILLIAM ZENTMAYER

Anatomy and Physiology

CORNEAL INNERVATION: CLINICAL CONSIDERATIONS. E. FORNES PERIS, Arch. Soc. oftal. hispano-am. **9:** 237 (March) 1949.

Fornes Peris has previously described in detail the structure, arrangement and nature of the corneal nerves. He was unable to demonstrate nerve filaments within the corneal epithelium after repeated staining by the Bielschowsky-Gros and Llombart-Jabonero silver methods, with which he obtained beautiful views of the plexuses and fine nerve fibrils situated below the basal epithelial cells.

The author correlates his observations with corroborating clinical conditions. Foreign bodies superficially located in the corneal epithelium may produce no symptoms until the tissue reaction manifests itself. The fact that the exposed cornea is in contact with floating particles in the atmosphere without the production of symptoms is also proof of the absence of superficial nerve endings on the cornea. The article is illustrated with diagrams and photomicrographs.

H. F. CARRASQUILLO.

Color Sense

PIGMENT-ANOMALOSCOPY: A NEW PROCEDURE FOR TESTING THE COLOR-SENSE. A. KETTESY, Brit. J. Ophth. **33:** 47 (Jan.) 1949.

An apparatus has been devised by Kettesy that mixes defined and measured pigment colors additively and allows these two mixtures to be compared simultaneously, as is done in Nagel's anomaloscope. Two parallel cylinders, on rotation around their axes, mix the colors of their surfaces. The cylinders can be pushed independently of each other to and fro during rotation. Two indicators moving on tape measures show the positions of each cylinder. The manner of use of the instrument is fully described.

W. ZENTMAYER.

Congenital Anomalies

RETROLENTAL FIBROPLASIA. V. E. KINSEY and L. ZACHARIAS, J. A. M. A. **139:** 572 (Feb. 26) 1949.

Studies were made of the number of premature infants born in particular hospitals in various locations. As a result of these studies, the authors reach the following conclusions: In certain areas the incidence of retrolental fibroplasia has increased significantly in recent years. In Boston, where the data are most complete, the rise in incidence was found chiefly in the 3 to 4 pound (1,361 to 1,814 Gm.) birth weight group. The greater frequency of retrolental fibroplasia correlates with several changes in treatment of premature infants, i. e., administration of

vitamin supplements in water-miscible form and increased use of iron. While a positive correlation between rise in incidence of the disease and change in treatment of premature infants does not constitute proof of any causal relation between the two, it is suggestive, nevertheless, that the medication used may be of etiologic significance. To test this possibility, the authors, in conjunction with the staffs of the Boston Lying-In Hospital and certain other hospitals, are planning to investigate the effect on the incidence of retrolental fibroplasia of omitting the iron, and also the multiple vitamin preparation in water-miscible form. It is planned to withhold the iron until the premature infant is between 2 and 3 months of age and to substitute for the multiple vitamin preparation vitamin D alone, in a water-miscible form (1,000 units daily). In addition, the diet will be supplemented with 50 to 100 mg. of ascorbic acid daily. No vitamin A or vitamin B complex will be given. The results of this study will be made available as soon as a sufficient number of infants have been tested to permit statistically valid conclusions concerning the true role of the aforementioned forms of treatment in producing retrolental fibroplasia.

This study has been concerned wholly with premature infants whose birth weights were less than 4 pounds (1,814 Gm.). The incidence of retrolental fibroplasia in heavier premature infants and in term babies has not been investigated, but, judging from the number of known cases of the disease among such infants, it must be extremely low. Before one draws inferences regarding possible harmful effects from the use of water-miscible vitamin preparations or of iron in treating heavier premature infants or term babies, one should consider these facts.

J. A. M. A. (W. ZENTMAYER).

AN UNUSUAL CONGENITAL DEFECT. A. H. BRIGGS and D. W. MCLEAN, Brit. J. Ophth. **33**: 381 (June) 1949.

The authors described a congenital anomaly in a girl 14 days old. The pregnancy and labor were apparently normal. Examination of the child at the age of 6 years revealed a large coloboma of the iris on the nasal side which was completely filled by a rounded pink mass with fine vessels running over its surface. Over the base of the tumor the cornea showed two islands of grayish opacity, resembling arcus senilis. Thin strands of pupillary membrane were present. Refraction revealed a high, irregular astigmatism. The disk showed situs inversus. There was complete absence of inflammatory reaction.

W. ZENTMAYER.

Conjunctiva

OPTIMAL METHODS IN THE TREATMENT OF OPHTHALMIA NEONATORUM. ARNOLD SORSBY and IRIS KANE, Brit. M. J. **2**: 562 (Sept. 10) 1949.

Sorsby briefly reviews his results with the sulfonamide drugs and with penicillin and finds that the percentage of failures was considerable in both series. In the present study, he reports on 151 new cases, with the following results: The intensive local application of penicillin is still the best method of penicillin therapy of ophthalmia neonatorum. The sulfonamides may be used to advantage in higher doses and a more rapid

response is obtained, the results being as rapid as those obtained with the intensive local use of penicillin. Contrary to expectation, the combined local use of penicillin and the oral administration of the sulfonamides did not seem to reduce the rate of relapse. Sulfamerazine is the sulfonamide of choice, as with it the frequency of unsatisfactory responses and relapses is reduced.

The routine procedure of treatment for both methods is then described. In a summary, it is stated that the oral administration of doses of 200,000 units of penicillin, either alone or after an initial intramuscular injection, has proved disappointing. The duration of the treatment was reduced by increasing the dose of the sulfonamide. Combined oral administration of the sulfonamide and local use of penicillin proved effective in reducing the duration of the treatment, but was ineffective in reducing the considerable frequency of relapses. The authors believe that the best way of administering penicillin is the instillation of drops in a concentration of 10,000 units per milliliter at intervals of one minute for one-half hour, and then at less frequent intervals. The best results with sulfonamide therapy were obtained with higher doses, i. e., sulfamerazine in a dose of 0.5 Gm. initially and then 0.25 Gm. at intervals of eight hours.

ARNOLD KNAPP.

SIMPLIFICATION OF THE OPERATION FOR PTERYGIUM. F. A. CHAVARRIA, Arch. Soc. oftal. hispano-am. **9**: 455 (April) 1949.

After enumerating the multiple surgical procedures used in dealing with pterygiums, Chavarria gives the following technic of his own, which, according to him, is the simplest of all and in his experience has the least often been followed by recurrences.

The usual local anesthesia is used, but he injects 0.5 cc. of 2 per cent procaine hydrochloride with epinephrine hydrochloride under the pterygium on the scleral side very close to the limbus. The growth is dissected from its corneal insertion with a very sharp cataract knife, being careful to leave no vestige of its tissue adherent to the cornea. The dissection is now continued on the sclera to an extent of 4 mm. from the limbus, the growth being cut at this level with a straight scissors perpendicular to the direction of the tissue fibers. With the same sharp knife, the uncovered scleral portion is curetted so as to leave it free from remnants of the tissue of the pterygium in the same way in which it was done in the cornea.

H. F. CARRASQUILLO.

Cornea and Sclera

PRESERVATION OF RABBIT CORNEA FOLLOWING EXPOSURE TO THE CAPACITRON. T. D. DUANE and O. S. LEE, Am. J. Ophth. **32**: 671 (May) 1949.

Duane and Lee stored rabbit corneas at room temperature for periods up to fifty-three days in ampules containing various mediums after exposure to the penetrating electrons of the "capacitron." Respiration and bacterial growth were inhibited. The gross appearance was not greatly altered. Corneal transplants performed with the treated corneas healed well but remained opaque.

The results are interpreted as representing a denaturation of the corneal proteins by the electrons from the "capacitron."

W. S. REESE.

REGENERATION OF THE CORNEAL STROMAL CELLS. A. E. MAUMENEE and W. KORNBLUETH, Am. J. Ophth. **32:** 1051 (Aug.) 1949.

Maumenee and Kornblueth found that rabbit cornea will regain its normal clinical and histologic appearance after most, if not all, of the stromal cells have been destroyed by freezing. The stromal cells die by nuclear fragmentation after freezing. Destroyed stromal cells are replaced by migration and multiplication of undamaged corneal corpuscles and by transformation of wandering macrophages.

W. S. REESE.

TREATMENT OF HYPOPYON ULCER OF THE CORNEA. E. H. CAMERON, Brit. J. Ophth. **33:** 368 (June) 1949.

Cameron describes the treatment used routinely in the cases of hypopyon at the department of ophthalmology of the Royal Infirmary of Edinburgh. The eye is kept free from secretion with a simple lotion, and atropine is instilled two or three times a day. Sodium sulfacetimide powder is applied a number of times a day, and during the night as well in severe cases. After light cocainization of the eye, the powder is heaped on the ulcer, and the lids are kept apart until the powder has dissolved. The number of applications is decreased as improvement occurs. After discharge, the patient uses drops of a sodium sulfacetimide solution during the rest of his convalescence. Since 1942, only 2 eyes have been lost. It has been found that when sodium sulfacetimide fails to produce early and rapid improvement, penicillin and other forms of treatment are rarely of much more help.

W. ZENTMAYER.

MODERN VIEWS OF SURGERY OF THE CORNEA. M. SOBHY BEY, Brit. J. Ophth. **33:** 372 (June) 1949.

Bey summarizes briefly the present trend in corneal surgery. He states his preference among the various procedures that have been suggested for prevention of imminent perforation of the cornea and the management of prolapse of the iris after perforation for adherent leukoma, conical cornea and ectatic irregularity of the cornea.

W. ZENTMAYER.

FUNCTION OF THE PRESERVATIVE ON THE HISTOLOGIC CHANGES OF CORNEAS KEPT IN THE ICE BOX AFTER KERATOPLASTY. S. SÉDAN-BAUBY, J. SÉDAN and H. PAYAN, Ann. d'ocul. **182:** 364 (May) 1949.

The authors review their previous statements on the use of preserved corneas. In this article they present the histologic evidence to substantiate some of their clinical results.

Four series of experiments were performed. In the first series the eyes were enucleated twenty-four hours after death. In the second, third and fourth series the eyes were enucleated immediately after the animal

was killed. The eyes were stored at 1 C. Some were kept in a humid atmosphere; one series were kept in a 10 per cent solution of the animal's citrated blood, and another series was kept in neutral liquid petrolatum U. S. P.

The histologic changes in the corneas in the different series are described in detail and are illustrated with photomicrographs.

In the corneas preserved in free air, the histologic changes were much more advanced in the eyes that were enucleated twenty-four hours after death than in those enucleated immediately after death. Preservation in citrated blood and in liquid petrolatum delayed the usual changes noted in the epithelium.

P. R. McDonald.

Technic in Penetrating Keratoplasty. J. J. Barraquer Moner, Arch. Soc. oftal. hispano-am. **9:** 152 (Feb.) 1949.

With an improved technic, the author has succeeded in eliminating almost completely the most dreaded postoperative complication of keratoplasty, anterior synechias.

The eye to be operated on must be free from any inflammatory activity. The cornea must be of normal thickness in the zone which is to surround the transplant, and the anterior chamber and intraocular tension must be normal.

The size of the transplant should be determined beforehand. Usually a transplant of 5 or 5.5 mm. diameter is sufficient, but occasionally one of 6 or 6.5 mm. diameter is necessary. Preliminary keratectomies may be necessary to equalize the thickness of the cornea to that of the transplant. The transplant must be of the same size as the resected piece of cornea, except in the case of myopia of corneal ectasia, in which it may be 1 mm. smaller. The pupil must be in miosis.

The stages in the operation are as follows: (1) orbicular akinesia, (2) retrobulbar injection, (3) trephining, (4) preparation of the transplant, (5) placement of the transplant in position and (6) suture of the transplant. When the patient is nervous or noncooperative, it is advisable to add a few drops of alcohol to the procaine solution used for akinesia, so that a 10 to 30 per cent concentration of the alcohol is obtained. Alcohol is also added to the 2 per cent solution of procaine hydrochloride with epinephrine hydrochloride used for the retrobulbar injection to make a 10 per cent concentration.

Two minutes after the retrobulbar injection is made, the trephining may be performed. The lids are retracted, and the eye is immobilized with a Barraquer-Lloveras fixation forceps. The author uses his own trephine. The trephine must be kept in a vertical position and its rotatory movements made with amplitude and a gentle, uniform pressure. In case the trephining is not completed properly, the Castroviejo scissors are used to finish the separation of the piece of cornea. Traction should never be exerted in detaching it.

After the trephining is completed, the transplant is prepared. This must be free from irregularities. With a fine forceps, the piece of pathologic cornea resected is removed and in its place the transplant is adapted. The fixation of the transplant by suturing is the most important step in the operation with respect to postoperative complications. The author uses direct suturing. He employs very sharp needles, with the

cutting edge downward. The needle enters the transplant, which is held with a Hess forceps by its anterior layers and is passed through the epithelial surface to emerge at the middle of the thickness of the transplant; it then is reinserted through the middle of the thickness of the recipient cornea to emerge at its epithelial surface. In 5 mm. transplants two sutures at the end of the 6 to 12 o'clock meridian are sufficient; in the 6 mm. transplants four or more sutures are necessary for good coaptation.

At the end of the operation the conjunctival sac is irrigated with isotonic sodium chloride solution, and a solution of physostigmine is instilled. Penicillin ointment is applied. A binocular bandage is used. The patient must be in bed for twelve days. The first dressing is made on the third postoperative day, and 1 drop of a 2.5 per cent solution of atropine is instilled. The stitches are cut at the end of fifteen days. The bandage is removed in twelve days in case of the 5 mm. transplant; in twenty days with the 6 mm. transplant in twenty-two days with the 6.5 mm. transplant.

The most difficult step in the operation is the suturing. A dark room with good focal illumination is necessary. The article is illustrated with diagrams and photographs.

H. F. Carrasquillo.

Treatment of Purulent Corneal Ulcers with Penicillin. N. Ivanov, Vestnik oftal. **28:** 25, 1949.

During 1948, 29 patients with corneal ulcers were treated with drops of penicillin solution (1,000 Oxford units to 1 cc. of isotonic sodium chloride solution) every two hours. The ulcers had been neglected, as 27 of the 29 patients came for treatment from the sixth to the twentieth day. Twenty-four patients had serpiginous ulcer; 2, catarrhal, and 3, trophic ulcers with secondary infection. The localization of the ulcer was central in 21 patients. In 18 patients hypopyon was present. Trauma was the most frequent cause, particularly in farmers. The bacteriologic findings were as follows: a diplococcus, in 11 cases; gram-positive bacilli, in 6 cases, and the staphylococcus or streptococcus, in the others. In 4 cases no smear was taken. In cases in which the ulcer occupied half or more of the cornea, paracentesis was performed with introduction of penicillin solution into the anterior chamber (5,000 Oxford units to 1 cc. of isotonic sodium chloride solution), and in 6 cases tarsorraphy was done. In 2 cases there was perforation of the cornea. The period of hospitalization was from seven to sixty-seven days.

The final visual acuity was below 0.1 in 14 patients, from 0.1 to 0.2 in 7 patients and above 0.2 in 8 patients.

The results were good, as many of these patients had vision equal only to light projection or finger counting at the time of admission.

O. Sitchevska.

Treatment of Scrofulous Keratitis with Tuberculin and Calcium Chloride. Z. Shuiskaya, Vestnik. oftal. **28:** 34, 1949.

A comparative evaluation of the desensitization with tuberculin and with intramuscular injections of calcium chloride was made on 50 patients with various forms of scrofulous keratitis—phlyctenular kera-

titis, infiltration of the cornea, with mild vascularization, and scrofulous pannus. The patients were predominantly young (from 10 to 30 years of age). In 24 patients no changes were found in the lungs; in 18 patients bronchoadenitis was present in the stage of induration, and in 8 patients changes in the lungs were seen on roentgenoscopic examination. The reaction to the Mantoux test was positive in all patients.

The tuberculin therapy was applied to one-half the patients after the Pandorf method (several scratchings of the skin of the forearm with rubbing in of old tuberculin), with an interval of six to eight days. Improvement in the subjective and objective symptoms was marked after one or two treatments. Blepharospasm and photophobia disappeared; infiltrates absorbed, and vessels of the cornea were obliterated after a few treatments. In 3 eyes there was a focal reaction in the form of new infiltrates. The general condition also improved under the tuberculin desensitization therapy.

Intramuscular injections of calcium chloride (0.25 per cent solution, 10 cc. daily for ten to twelve injections) were given to the other 25 patients. There was no general reaction, but the desensitizing action was noted only after several injections, as the irritability of the eyes diminished rapidly, the patients gained in weight and they remained in the hospital a much shorter period than those treated with tuberculin. The Mantoux reaction remained positive for all patients receiving either method of treatment.

Shuiskaya gives preference to calcium chloride therapy, as the dosage is easier to maintain than in the tuberculin therapy and there are no contraindications to it, as there are to tuberculin therapy.

O. Sitchevska.

General

A Survey of Anterior Segment Photography. E. S. Wright, Am. J. Ophth. **32**: 1245 (Sept.) 1949.

Wright presents an elementary review of photographic optics. Lighting methods are enumerated, methods of photography of the anterior segment of the eye are detailed, and the advantages and disadvantages are set forth. A method of converting any ordinary camera to one equipped for anterior segment photography is described.

W. S. Reese.

Some Observations on the Causation and Elimination of Sattler's Veil. H. Treissman, Brit. J. Ophth. **33**: 555 (Sept.) 1949.

Corneal veiling must not be treated as an isolated symptom but is inevitably bound up with the subject of the fitting of contact lenses. It is due to defects in fitting which give rise to circulatory obstruction of various degrees of severity or to stagnation of the precorneal fluid or to both. Stagnation of the precorneal fluid alone will give rise to slight veiling without intolerance, the veiling usually being noticed only in artificial light. When combined with circulatory embarrassment, veiling is severer and is accompanied with irritability and intolerance. The remedy lies in correcting or avoiding the defects, not in relieving their consequences by drilling holes in the lens. All the untoward symptoms

associated with contact lenses, veiling included, can be avoided by bringing the practice of fitting out of the academic and theoretic clouds down to solid earth. Treissman makes a plea for more rationalism in the fitting of contact lenses. To obtain as nearly as possible uniformly satisfactory results, one must fit lenses as large as is consistent with free movement of the eye. This means molded lenses, with capillary clearance everywhere except for adequate limbal clearance. According to the author, the reputation of contact lenses is, so far as the wearing public is concerned, rapidly declining.

W. ZENTMAYER.

INFLUENCE OF SEASONAL CHANGES ON FREQUENCE OF CERTAIN OCULAR DISEASES. E. B. STREIFF and J. F. CUENDET, Ann. d'ocul. **182:** 329 (May) 1949.

The authors discuss the seasonal variation of rheumatic iridocyclitis, detachment of the retina, acute glaucoma, marginal corneal ulcer, keratoconjunctivitis, herpetic keratitis and the various forms of conjunctivitis.

The first part of the paper deals with the statistical compilation of their data. The individual diseases are then discussed, and the monthly seasonal variation is shown in graphic form.

The article concludes with a discussion of the factors in the susceptibility of the organism to the rhythmic changes in the season.

P. R. MCDONALD.

RESISTANCE OF OCULAR TISSUES TO HIGH FREQUENCY CURRENTS. G. MEYER-SCHWICKERATH, Arch. f. Ophth. **149:** 288 (April) 1949.

The author has measured the resistance of whole eyes and isolated ocular tissues to high frequency currents of varying wavelengths. Most suitable for electrocoagulation in treatment of retinal detachment are currents of 100 to 400 meter wavelengths. Such currents are accurately measurable. An instrument that generates such currents is described.

P. C. KRONFELD.

General Diseases

OCULAR COMPLICATIONS OF TEMPORAL ARTERITIS. C. SMITH and P. B. GREENE, Am. J. Ophth. **32:** 685 (May) 1949.

Smith and Greene report 4 cases of temporal arteritis. They remark the discrepancy between the severe visual loss and the few changes in the fundus.

W. S. REESE.

PATHOGENESIS OF CONCURRENT EYE AND JOINT DISEASES. E. GODTFREDSEN, Brit. J. Ophth. **33:** 261 (May) 1949.

A clinical analysis is given of the incidence and symptomatology of concurrent diseases of the eyes and joints. The medical diseases of joints which are complicated by ocular symptoms (phlyctenular conjunctivitis, scleritis, iritis and keratoconjunctivitis sicca) all belong to the type of infective arthritis, partly acute and partly chronic (rheumatic fever, gonorrheal arthritis, Reiter's disease, multiple rheumatoid arthritis and ankylopoietic spondylitis). The pathogenesis is presumably the same

for the ocular and for the joint disease, being probably an allergotoxic reaction to a primary bacterial or virus infection. This hypothesis is borne out by clinical points of resemblance to various generalized diseases affecting the joints, skin and pluriorificial mucous membranes (conjunctivitis, stomatitis and inflammation of the external genitalia), in which an allergotoxic pathogenesis is certain or probable—Stevens-Johnson syndrome, Behcet's syndrome, foot and mouth disease, serum disease, acute disseminated erythematous lupus and intoxication by heavy metallic salts, notably sanocrysin® (gold and sodium thiosulfate) and the arsenicals.

W. ZENTMAYER.

TOXOPLASMOSIS. ANNOTATION, Brit M. J. **1**: 718 (April 23) 1949.

This review is based principally on the article by Wolf and his colleagues (ARCH. OPHTH. **29**: 1 [Jan.] 1943) and a second article by Binkhorst (*Ophthalmologica* **115**: 65, 1948). In children the usual symptoms of toxoplasmosis consist in meningoencephalomyelitis, involvement of the eye in the form of bilateral chorioretinitis in the central area of the fundus and cerebral calcification, noticeable on roentgenograms of the skull. The chorioretinal lesions are healed and appear as atrophic pigmented areas, resembling macular colobomas. The onset of toxoplasmosis is very early in life, and a definite diagnosis can be made by finding the protozoon at biopsy or necropsy, either directly or after passage through animals. This had been accomplished, according to Binkhorst, in 18 cases up to 1945; 13 of these were of congenital and 5 of acquired infections.

As chorioretinitis is unusual in children, its presence in a case of encephalitis should suggest the possibility of toxoplasmosis, particularly if cerebral calcification is present. This would also apply to the case of a mentally defective child or a child with cerebral spastic infantile paralysis (Little's disease). In Binkhorst's report there is a history of a child of 6 years who was brought to the hospital for treatment of convergent strabismus. Microphthalmos and chorioretinitis were present, and roentgenograms of the skull showed multiple small and large opacities. Micro-organisms resembling toxoplasmas were found in a cerebral granuloma in a guinea pig after intracerebral injection of cerebrospinal fluid from the patient.

The article concludes with the statement that "toxoplasmosis must be more common in human beings than is thought and it should be considered as a possible cause of visual disability in children in whom no direct interference with the light path is immediately noticeable."

ARNOLD KNAPP.

REITER'S DISEASE. E. CASS, Arch. Soc. oftal. hispano-am. **9**: 176 (Feb.) 1949.

The syndrome of enteritis, urethritis, polyarthritis and ocular symptoms (usually conjunctivitis and iritis) known as Reiter's disease is discussed, and a case is reported in a man aged 24. The patient was suffering from nonspecific urethritis. A few days afterward there developed bilateral conjunctivitis free from micro-organisms, which was followed by arthritis of the knee joint. The latter promptly disappeared with physical therapy. Shortly afterward interstitial keratitis appeared in the right

eye and later severe iritis developed in the left eye. The results of all laboratory examinations were noncontributory. The author states that this case is the only reported instance of the syndrome in which interstitial keratitis was present. H. F. CARRASQUILLO.

Glaucoma

THERAPEUTIC RESULTS IN ADVANCED CHRONIC SIMPLE GLAUCOMA WITH TELESCOPIC FIELDS. S. BLOOMFIELD and L. KELLERMAN, Am. J. Ophth. **32:** 1177 (Sept.) 1949.

Bloomfield and Kellerman studied 41 eyes with uncontrolled chronic simple glaucoma and central fields reduced to 10 degrees from fixation at their widest meridian. Approximately one-half these eyes were operated on. Comparison of the treated and the untreated eyes suggests that operation in cases of this type of glaucoma is contraindicated, since the eyes not operated on, in spite of inadequately controlled tension, retained central vision for long periods. W. S. REESE.

TRAUMATIC OR "CONCUSSION" CHRONIC GLAUCOMA. A. D. 'OMBRAIN, Brit. J. Ophth. **33:** 495 (Aug.) 1949.

The author presents the records of 3 cases selected from a series of 37 cases of unilateral chronic glaucoma in which there was a history of trauma. In all cases the glaucoma was of the true chronic progressive noninflammatory type. The delay in the onset of symptoms was from a few weeks to many years after the date of injury; this, however, may indicate merely the delay in discovery of the condition. The injuries included blows on the eye itself; injuries to the skull, in general causing either fracture or concussion of the brain, and heavy falls. The author believes that the glaucoma is the result of concussion produced either by direct trauma to the cornea or by the pressure of suddenly compressed aqueous humor. He draws the following conclusions: One should not too hastily diagnose chronic glaucoma in one eye as a primary, and therefore eventually bilateral, disease, for a careful case history may reveal it to be a lesion affecting only one eye, and secondary to concussional trauma. Probably in some cases bilateral chronic glaucoma may have its origin in the shock of a concussional trauma.

W. ZENTMAYER.

THE SUBCONJUNCTIVAL AB EXTERNO APPROACH IN GLAUCOMA. E. WOLFF, Brit. J. Ophth. **33:** 514 (Aug.) 1949.

A small, exceedingly sharp scalpel is used to make the incision into the anterior chamber. The iris inclusion is accomplished by a modification of the Holth operation 2. An important point in the prevention of closure is to start massage immediately. The operation is relatively easy to perform; there is practically no danger of injury to the lens; the anterior chamber is usually reformed the day after the operation; postoperative iritis is rare, and no instrument enters the eye. A diffuse area of drainage is produced, so that infection is much less likely to occur than with a localized bleb. W. ZENTMAYER.

Injuries

INTRAOCULAR FOREIGN BODIES. J. P. MCBRIDE, Am. J. Ophth. **32:** 1255 (Sept.) 1949.

McBride gives the data on 50 consecutive cases of intraocular foreign body. He discusses procedures for locating intraocular foreign bodies and methods for their removal. He finds the Berman locator a valuable supplement to present methods.

W. S. REESE.

ON THE USE OF AMNIOTIC MEMBRANE. C. DANSEY-BROWNING, Brit. J. Ophth. **33:** 518 (Aug.) 1949.

After the removal of a benign melanoma of the bulbar conjunctiva, a piece of sterile amniotic membrane (fat free, Morley's process), of the same size as that of the raw area, was sutured into position. The progress in the case is shown by illustrations. The results indicate a possible use for amniotic membrane in the early treatment of ophthalmic wounds in wartime, particularly in the mobile ophthalmic units.

W. ZENTMAYER.

UNUSUAL OCULAR FOREIGN BODY. NIRMAL KUMAR GHOSE, Brit. J. Ophth. **33:** 520 (Aug.) 1949.

During the examination of a patient with irritability of the eye and deep orbital pain, which came on after he had washed his face in a pond, a snail emerged apex first from under the lower conjunctival fornix. The preauricular gland was enlarged. The cornea showed subepithelial infiltration. The snail was identified as a young Viviparus bengalensis. The author believes the snail was embedded by the patient's having given the eye a good rub.

W. ZENTMAYER.

Lens

CATARACT AND TETANY PRODUCED BY PARATHYROID DEFICIENCY DURING PREGNANCY, LACTATION AND MENSTRUATION. D. J. LYLE, Am. J. Ophth. **32:** 1183 (Sept.) 1949.

Lyle reports a case of idiopathic parathyroid insufficiency and describes the course of this disease as the patient passed through pregnancy, lactation and menstruation. He concludes that the increased demand for calcium during pregnancy, lactation and menstruation may change an asymptomatic, latent parathyroid deficiency into a symptomatic, manifest hypoparathyroidism, with serious consequences to vision through ectodermal damage, both neural and somatic. These complications can be averted by routine examination during early pregnancy and lactation. Treatment, once the symptoms have appeared, may arrest, but cannot entirely restore, the visual loss.

W. S. REESE.

DEVELOPMENT OF COMPLICATED CATARACT. B. DAVIDS, Arch. f. Ophth. **149:** 156 (April) 1949.

The author describes histologic changes in the lens of the eyes of rabbits in which severe persistent iridocyclitis had been produced by the injection of a pure culture of Bacillus subtilis into the anterior chamber.

Damage had occurred to the anterior layers of the lens as the direct result of an adjacent inflammatory focus. Besides, "remote" effects could be recognized in the posterior layers of the lens. These changes resembled closely those seen in complicated cataract of man. The author stresses the histologic similarity of complicated and radiation cataract.

P. C. KRONFELD.

Neurology

CHANGES OF THE FUNDUS IN CHILDREN WITH TUBERCULOUS MENINGITIS TREATED WITH STREPTOMYCIN. S. KOTLIAREVSKAYA and A. DOBROGAYEVA, Vestnik. oftal. **28:** 21, 1949.

Seventy-five children with tuberculous meningitis, aged from 5 months to 14 years, were under observation from one to eleven months. Of these, 45 were treated with minimal doses of streptomycin (0.02 to 0.05 Gm.), injected into the suboccipital region, as well as intramuscularly. Seventeen children died during the first three months of treatment, and 7 children, during the fourth to the eleventh month of hospitalization. The treatment with streptomycin changed the course of the disease. In some cases the disease was retarded, but after a prolonged remission the children died of an exacerbation of the tuberculous meningitis. Funduscopic examination revealed solitary tubercles in 6 children, tubercles and papilledema in 8 children and papilledema only in 16 children. In 15 children no changes in the fundus were seen. The tubercles were observed in various stages of the disease, frequently when the clinical symptoms of meningitis had subsided under the treatment with streptomycin, the spinal fluid was clear and the child felt rather well.

In 2 children the appearance of solitary tubercles was noted simultaneously with inflammatory changes in the spinal fluid, with subsequent exacerbation of the meningeal symptoms one to two months later. In 1 of these patients the tubercle appeared on the one hundred and thirty-seventh day of the disease, after the fourth course of treatment with streptomycin. In 2 children the tubercles appeared in the choroid at the initial stage of the disease, during the first course of treatment with streptomycin. In a group of 16 children papilledema was observed before treatment was started. Although streptomycin therapy influenced favorably the general course of the meningitis, the fundus signs remained unchanged. In a group of children not treated with streptomycin no changes in the fundus were observed, as they died within two or three weeks.

Thus, streptomycin retards the progress of tuberculous meningitis but does not prevent the fatal outcome. At the same time, the changes in the fundus are observed more frequently because of the retardation in the course of the disease.

O. SITCHEVSKA.

Ocular Muscles

SUGGESTIONS FOR THE SURGICAL MANAGEMENT OF STRABISMUS. L. T. POST, Am. J. Ophth. **32:** 345 (March) 1949.

Post briefly reviews the history, examination and treatment of squint and discusses the surgical technic. He advises a thoughtful and complete study of each case of strabismus before surgical intervention. The role

of the vertical rectus muscles in producing the defect should be carefully analyzed and a two stage operation performed in cases in which both lateral and vertical deviations occur. W. S. REESE.

FINAL RESULTS OF SQUINT OPERATIONS, IN WHICH RESTORATION OF BINOCULAR SINGLE VISION WAS NOT EXPECTED. A. STANWORTH, Brit. J. Ophth. **33**: 477 (Aug.) 1949.

The purpose of this paper is the analysis of the results of operation in cases of squint in which restoration of binocular single vision was not expected, particularly with regard to the final state of binocular vision. Of the original 155 cases, in all of which it was considered that orthoptic treatment was unlikely to benefit the patients or in which it had already been tried and abandoned, satisfactory preoperative and postoperative tests for analysis had been performed in 100. In 26 per cent fusion or stereopsis developed, the favorable factors being the presence of simultaneous perception before operation, approximately equal vision in the two eyes, age of onset at 3 years or more and a small postoperative angle. Of the cases fulfilling these criteria, fusion or stereopsis developed in 76 per cent, although in most instances preoperative orthoptic treatment had been given without benefit. It appeared that those patients who were going to acquire good binocular vision did so within one year of operation. The magnitude of the preoperative angle of deviation and the age at operation (from 6 years upward) was of no significance. The bearing of these results on the treatment of squint is discussed, a trial of earlier operation with careful follow-up examinations being suggested.

W. ZENTMAYER.

SURGERY OF THE INFERIOR OBLIQUE MUSCLE: INDICATIONS, TECHNIC AND RESULTS. M. LOUTFALLAH, Ann. d'ocul. **182**: 81, 1949.

The author reviews the functions of the muscles which raise and lower the eyes. He points out the great difficulties that are sometimes encountered in establishing a diagnosis as to which muscle or muscles are involved. One must at times differentiate an actual paresis, inhibitional palsy and secondary contractures of a homolateral antagonist. One must also consider the primary and secondary actions of a muscle before deciding on any surgical procedure.

The surgical anatomy and physiologic action of the inferior oblique are discussed in detail. Then follow a list of the types of operation, the indications for operation and the detailed operative technic. The author concludes with a discussion of the results he obtained in a series of thirty-eight operations on the inferior oblique. The article is well illustrated and there is a complete bibliography, of fifty-two references.

P. R. MCDONALD.

Operations

SURGICAL REPAIR OF NEUROFIBROMATOSIS OF EYELID. M. M. KULVIN, Am. J. Ophth. **32**: 1231 (Sept.) 1949.

Kulvin discusses surgical repair of neurofibromatosis of the eyelid and reports 2 cases, with a description of the methods used. The article contains a number of illustrations. W. S. REESE.

A Preliminary Note on a New Method of Fixing Corneal Grafts. C. A. Pittar, Brit. J. Ophth. **33:** 567 (Sept.) 1949.

A trephine guide is placed on the cornea and fastened with unknotted sutures. The trephine is then placed in the aperture in the guide, and a cut perhaps one third of the way through the cornea is made.

The trephine and the guide are then removed, and the trephining is completed. When the graft is set in place, the splint is applied and the sutures used to hold the trephine guide are tightened over the arms of the splint and the knots completed. The guide and the splint are made of platinized gold and are 0.2 mm. thick. The advantages claimed for this method of procedure are a more perfect sealing of the wound with prevention of tilting of the graft; prevention of sudden loss of the anterior chamber after it has reformed; greater accuracy and even distribution of pressure over the whole wound, and simpler technic with assured perfect placing. The results obtained in 3 cases are illustrated.

W. Zentmayer.

Parasites

Ocular Onchocerciasis. M. Puig Solanes, B. R. Noble and A. Fonte, Am. J. Ophth. **32:** 1207, (Sept.) 1949.

Puig Solanes, Noble and Fonte report ocular infection in 60 to 77.2 per cent of 1,000 cases of onchocerciasis (filariasis) occurring in Mexico. Caucasians were less susceptible, whereas those of mixed racial stock were most susceptible. The diagnosis is made on the following basis: (1) a history of residence in the affected areas of Mexico, Guatemala and Africa; (2) clinical symptoms and signs of nodules; (3) identification of the microfilarias in the eye with the slit lamp and in the cutaneous nodules by means of the microscope. Examination of the nodules is considered the most reliable method.

W. S. Reese.

Pharmacology

Effect of Priscol® (Benzazoline) on the Normal and the Diseased Eye. H. Fanta, Arch. f. Ophth. **149:** 199 (April) 1949.

Benzazoline (priscol®) (benzazoline; 2-benzyl-4,5-imidazoline hydrochloride) is a synthetic compound related in structure to histamine. It has found wide acceptance in many branches of medicine as a powerful vasodilator, especially of the small arteries. After intravenous or retrobulbar injection, it causes a measurable widening of the retinal arterioles. Benzazoline (priscol®) is marketed as a 5 and 10 per cent solution for local use, in ointment form and as tablets for oral use. On retrobulbar injection, it causes a measurable transient widening of the color fields in normal eyes. Similar improvements are reported in cases of organic retinal and retinovascular disease. The effect on the retinal arterioles is, of course, transient. For the treatment of embolism of the central artery, the author recommends retrobulbar injection of benzazoline together with inhalations of amylnitrite. Benzazoline has proved of definite value in the treatment of retrobulbar neuritis, of quinine and methyl alcohol poisoning and related conditions.

P. C. Kronfeld.

Physiology

STUDIES ON THE INTRAOCULAR FLUIDS: I. THE REDUCING SUBSTANCES IN THE AQUEOUS HUMOR AND VITREOUS BODY. SIR STEWART DUKE-ELDER and H. DAVSON, Brit. J. Ophth. **33**: 21 (Jan.) 1949.

These authors now agree that the concentration of glucose in aqueous and in vitreous humor is lower than that in blood. They believe the deficiency of glucose in the aqueous is due to its utilization by the lens and that the deficiency of glucose in the vitreous is due to the utilization of the sugar by the retina, since the ultrafiltrate from the blood must first pass through the retinal tissue before it gets into the vitreous. That the lens uses glucose is attested to by the fact that in cats the concentration of sugar in the aqueous humor increased by about 25 per cent after extraction of the lens. In the rabbit, however, this increase was much smaller, and in 1 case there was an actual decrease in the concentration of glucose found. However, the vitreous also showed a decided increase in the aphakic eye in cats and a smaller increase in rabbits. It should be noted that these authors measured total reducing substances in the aqueous and vitreous, of which ascorbic acid, as well as glucose, must play a part. The authors then confirmed previous work which showed that the distribution of glucose through the vitreous was not uniform, but that the peripheral posterior part of the vitreous contained less sugar than the central core. The authors believe that the retina must draw on glucose in the vitreous body when the retinal and uveal circulations are cut off.

Studies on the concentration of glucose in plasmoid aqueous show that the aqueous as it is reformed after paracentesis differs from plasma in its sugar content by only about 5 per cent.

In a further series of experiments, the authors measured the rate of penetration of various sugars into the aqueous humor and the vitreous body in cat eyes. The penetrations of glucose, galactose, free methyl glucose and xylose were the same. Sucrose penetrated much more slowly, and polysaccharides, such as inulin and raffinose, were found to be unable to cross the blood-aqueous barrier in significant amounts in the normal state. The rates of penetration of all these sugars into the vitreous were lower than of those into the aqueous, so that the authors believe there is a more selective barrier to the diffusion of these sugars into the posterior part of the eye than into the aqueous humor. Evidence indicated a considerable amount of diffusion of sugar into the anterior chamber from the iris, and evidence is presented which suggests that the diffusion of sugars into the vitreous body is not confined to the ciliary body but occurs from all the surrounding vascularized tissues. There is strong evidence that the entry of all of the sugars into the eye can be explained on the basis of the process of diffusion and that it is not necessary to invoke a secretory mechanism.

F. H. ADLER.

PUPILLOPERIMETRY. H. HARMS, Arch. f. Ophth. **149**: 1 (April) 1949.

For a number of years Harms has been engaged in quantitative studies of the pupillary responses to accurately measurable light stimuli acting on circumscribed retinal areas. The principle underlying such

studies is that the receptor function for pupillomotor responses is probably just as significant a function of the retina as its ability to act as the receptor for light, form and color sensory stimuli. Moreover, measurements of the pupillomotor sensitivity of representative portions of the retina (pupilloperimetry) has the great advantage of objectivity over all strictly visual measurements. For those reasons, Harms has pursued his studies and refined his methods. In this paper, dedicated to Karl Wessely on the occasion of his seventy-fifth birthday, Harms reviews the history of pupilloperimetry, describes his present technic and reports some remarkable results. His instrument is, in principle, a perimeter with a standardized light source within a small box mounted on the perimeter arc. The intensity of the stimulus is varied by means of an iris diaphragm and Tscherning's photometric glasses. The duration of the stimulus is one second, during which the examiner watches the examinee's pupil through a telescope, which is also mounted on the perimeter. The smallest amount of light that causes a perceptible contraction of the pupil is considered the pupillomotor threshold for the particular retinal area in its particular state of adaptation. With this setup, the author has succeeded in demonstrating the blindspot in most of the cases tested. He has also found that in normal eyes the pupillomotor sensitivity parallels form sensitivity, that is, increases at a definite rate from the periphery toward the center. Even under conditions of dark adaptation, the center of the retina possesses greater pupillomotor sensitivity than any peripheral portion. Dark adaptation, however, does raise the pupillomotor sensitivity to some extent. "These findings suggest that only the cones act as pupillomotor receptors in man."

The author's findings in cases of homonymous hemianopsia are remarkable in that the pupillomotor sensitivity of the affected retinal halves proved to be diminished at the same rate as the light sense, in infrageniculate, as well as in suprageniculate, lesions. "Hemianoptic fixation of the pupil cannot be considered a definite sign of infrageniculate lesions. Further studies are necessary to determine whether the degree of loss of pupillomotor sensitivity is greater with infrageniculate than with suprageniculate lesions." The pupillomotor disturbances which the author reports in lesions of the visual cortex may be due to the absence of physiologic cortical influences on the retina or the lateral geniculate bodies. Pupilloperimetry promises to be a valuable method for the diagnosis of malingering.

P. C. KRONFELD.

Refraction and Accommodation

A FURTHER, VERY DELICATE TEST FOR ASTIGMATIC AXIS, USING THE CROSS CYLINDER WITH AN ASTIGMATIC DIAL AND WITHOUT USE OF LETTER CHARTS. W. CRISP and G. STINE, Am. J. Ophth. **32:** 1065 (Aug.) 1949.

Crisp and Stine suggest the use of the cross cylinder and a rotating cross controlled with a pulley mechanism to determine the astigmatic axis accurately.

W. S. REESE.

MODIFICATION OF TELESCOPIC SYSTEMS BY THE USE OF CONTACT LENSES. H. SAUTTER, Arch. f. Ophth. **149:** 142 (April) 1949.

A Galilean telescope can be "constructed" in front of the human eye by means of a contact lens with a minus power of about 30 D. combined with a spectacle lens of about + 20 D. (Bettman, J. W., and McNair, G. S.: *Am. J. Ophth.* **22:** 27, 1939). The author has made a theoretic study of the optical qualities of such systems and has also tried them out on a small number of patients with reduced visual acuity. The contact lens makes telescopic systems of the Galilean type more practical. The visual field is considerably widened, especially if a well corrected spectacle lens is used. A magnification of from two to three times is attained.

P. C. KRONFELD.

Retina and Optic Nerve

THE ARTIFICIALLY PRODUCED RETINAL PULSE. N. PINES, Brit. J. Ophth. **33:** 579 (Sept.) 1949.

In this interesting communication, Pines gives a full description of the artificially produced retinal pulse. He notes the impossibility of collapsing the retinal arteries, in contrast to the abolition of pulsation in the arteries on the disk. This remarkable fact, hitherto observed only by Baillart, but not explained by him, is accounted for by the active buffer effect of the retinal capillary bed.

W. ZENTMAYER.

PATHOGENESIS AND TREATMENT OF DIABETIC RETINOPATHY. A. MORÉU, Arch. Soc. oftal. hispano-am. **9:** 139 (Feb.) 1949.

The author states the belief that there are no lesions characteristic of diabetic retinopathy. In the majority of patients there is some allied vascular sclerosis or hypertension. In his experience, the condition subsequently presents the following ophthalmoscopic lesions: (*a*) small, deep-seated, punctiform hemorrhages; (*b*) degenerated zones, similar to those seen in Fuchs's circinate retinitis, and (*c*) larger hemorrhages, with great tendency to proliferative retinitis.

The exudates sometimes observed are not considered characteristic and are taken as symptoms of the accompanying hypertension.

The retinopathy of diabetes is at times discovered unexpectedly because of the presence of a central retinal hemorrhage. Usually it is found incidentally when the fundus is observed for some reason.

There is no relation between the presence of the retinal lesions and the sugar content of the blood. With a normal sugar content the diabetic retinopathy may continue to progress. The routine use of insulin for the retinal complication is not recommended.

Experimentally, hypoglycemic states induced in animals by the administration of large doses of insulin have brought about anatomicopathologic changes of the vascular and circulatory type in the cornea, anterior chamber, uvea and retina. The same changes, but less extensive, have been brought about by a diet lacking in carbohydrates. This proves, according to the author, that the use of insulin and the hypoglycemia together bring about circulatory changes, which later may result in anatomic alterations.

The association of diabetic retinopathy and hypertension is discussed. It is the author's experience that the diabetic patient always shows some alteration in tension, although not always a true hypertensive state.

The minute hemorrhages constant in diabetic retinopathy are related to capillary permeability. The author has found a diminished capillary resistance in diabetic patients with retinopathy.

The possible bearing of the mucopolysaccharide hyaluronic acid, present in the tissues, and especially in the vitreous, and its reducing enzyme hyaluronidase in the production of the retinal lesions of diabetes is analyzed. The inhibitory action of vitamin P derivatives on the enzyme is also mentioned. The altered carbohydrate metabolism may influence the hyaluronic acid–hyaluronidase equilibrium and give rise to the retinal pathology of diabetes.

Insulin should be used cautiously and given only in extreme cases. The capillary fragility should be treated with vitamin P. However, in the presence of hemorrhages neither this vitamin nor insulin should be given, except for some vital purpose. Heparin should be used in these cases.

H. F. Carrasquillo.

Therapeutics

Effect of the Diaminodiphenyl Sulfonamides on the Ocular Complications of Leprosy. A. Urrets Zavalia, Arch. Soc. oftal. hispano-am. **9:** 160 (Feb.) 1949.

The author reports the results of his observations during two years on patients in the dermatologic dispensary of Cordova with respect to the effect of the sulfonamides on the ocular complications of leprosy. Twenty-five patients were studied. He arrives at the following conclusions: 1. With use of the sulfonamides it is possible to avoid the development of ocular complications in patients who would otherwise show them. 2. On the other hand, treatment with the drug may produce mild acute iritis in these patients. 3. The new therapeutic agent in the doses used by him cannot check the evolution of torpid, progressive ocular lesions.

A table descriptive of the types of leprosy, the ocular pathology, the doses of the sulfonamides administered, the period of treatment and the changes in the general condition and, in particular, the ocular lesions in the 25 cases studied is presented.

H. F. Carrasquillo.

Treatment of Psychogenic Amaurosis. H. Koch, Arch. f. Ophth. **149:** 282 (April) 1949.

In several cases of psychogenic amaurosis the response to one or two electric shock treatments was good and lasting. The two poles of an alternating current (voltage and amperage not stated) were applied to the temples for a fraction of a second. The immediate effect resembled a severe epileptic seizure. As soon as the patient regained consciousness, his ability to see was demonstrated to him by means of a near vision chart with lines of gradually decreasing size. For patients with a milder disturbance the author recommends brief anoxia produced by the inhalation of nitrogen or by nitrous oxide anesthesia.

P. C. Kronfeld.

ACTION OF VITAMIN D_2 [CALCIFEROL] IN DISEASES OF THE EYE OF TUBERCULOUS ORIGIN. A. DOBROSMYSLOV, Vestnik. oftal. **28**: 24, 1949.

Observations were made on the action of vitamin D_2 (calciferol, or irradiated ergosterol) on tuberculous diseases of the eye in two series of patients. One series consisted of 10 patients, 6 of whom had uveitis and keratoscleritis and 4 phlyctenular keratoconjunctivitis. All received 200,000 units of calciferol a day for a period of twelve days to two months. Simultaneously, desensitizing treatment with calcium administered by intravenous injection and iontophoresis and proper diet was applied. In 6 patients exacerbation of the disease was produced, evidenced by increase in the ciliary injection, photophobia and keratic precipitates, as well as by nausea, diarrhea and subfebrile increase in temperature. The intensity of the Mantoux reaction was also increased during the treatment with calciferol. Thus high doses of the vitamin in this group produced sensitization in the form of activation of the ocular process and increase in the intensity of the Mantoux reaction.

In the second series, of 7 patients, the dose of calciferol was decreased to 20,000 units per day for a few weeks. No change in the course of the ocular disease was observed, but the intensity of the Mantoux reaction was decreased considerably.

In 3 patients with allergic scrofulous disease of the eye there was considerable clinical improvement in the eye under the vitamin therapy.

Laboratory data indicate that the calcium content of the urine is increased during treatment with the vitamin. Most likely the change in the sensitivization depends not on the calcium content of the blood but on the change in the calcium metabolism; i. e., with large doses of the vitamin a decrease of calcium salts occurs, but with smaller doses there is an accumulation of calcium salts in the organism.

The lowering of specific sensitivity of the organism with smaller doses of the vitamin permits the application of tuberculin therapy to tuberculous diseases of the eye.

O. SITCHEVSKA.

Tumors

OCULAR LYMPHOMAS. P. HEATH, Am. J. Ophth. **32**: 1213 (Sept.) 1949.

Heath found the commonest cytologic type in this series to be the lymphocytoma. Other cell types, that is, lymphomas of the lymphoblast, reticulum cell and plasma cell types, are also noted. The prognosis is not materially altered by the cell type. The lymphomas occur oftenest in the first decade and after the fifth decade of life. They respond to roentgen radiation in small doses and to excision when size permits. Long periods of remission may follow treatment. Lymphomas of the lid and orbit are like those occurring elsewhere. If early, small, discrete and primary, the immediate effects of removal and roentgen therapy are good; the remote effects are poor.

The series of lymphomas of the conjunctiva offer features similar to those of the series previously reported before by Schulz and Heath (*Radiology* **50**: 500, 1948), namely, that the primary lymphomas of the orbit and conjunctiva are rare and represent less than 1 per cent of a

total series of 1,671 ocular tumors. The primary conjunctival lymphoma is relatively benign if there has been no extension of the process at the time of treatment. A long interval may elapse before general involvement takes place. If the conjunctival lesion is extending and sarcomatous, the prognosis is in time invariably fatal.

W. S. REESE.

LEIOMYOMA OF THE IRIS. K. O'DAY, Brit. J. Ophth. **33**: 283 (May) 1949.

O'Day reports a case of leiomyoma of the iris occurring in a woman aged 65. Vision of the right eye had been failing for twelve months. The growth was sessile and gray and occupied the whole of the lower outer quadrant of the iris. It was very vascular and surrounded by a gelatinous fringe. The lens was opaque behind the tumor, and the opacity was spreading. The eye was enucleated. The tumor had all the characteristics of a leiomyoma. It was impossible to say from which muscle the tumor arose. Some sections appeared to show the cells of the dilator muscle elongating, gradually losing their pigment content and merging into a general stroma of the tumor. The situation of the tumor in the lower half of the iris, in all cases reported, adds weight to Verhoeff's suggestion that in his case the tumor originated from stroma cells of the embryonic uvea, possibly from misplaced cells which ordinarily would have taken part in the formation of the ciliary muscle. O'Day suggests that the tumor had arisen near the fetal fissure and that the origin may be traced to a defect arising at the time of its closure. This suggestion was earlier made by E. C. Moulton Jr. (*Am. J. Ophth.* **31**: 214 [Feb.] 1948), but that was unknown to the author at the time his paper was submitted for publication.

W. ZENTMAYER.

Society Transactions

EDITED BY DR. W. L. BENEDICT

NEW YORK ACADEMY OF MEDICINE, SECTION OF OPHTHALMOLOGY

Wendell L. Hughes, Chairman

Isadore Givner, M.D., Secretary

Nov. 15, 1948

ROUND TABLE DISCUSSION: "PROBLEMS IN OPHTHALMOLOGY"

QUESTION: Dr. Dunnington will you discuss surgery of the eye in the presence of endothelial dystrophy of the cornea?

DR. JOHN H. DUNNINGTON: Endothelial dystrophy of the cornea (cornea guttata) is not uncommon. It has been observed in about 4 per cent of all adults (Goar). It usually begins about the third decade of life and slowly increases with advancing age. Any intraocular operation seemingly increases the severity of the process. When it is present, particularly in the advanced stage, an uneventful cataract extraction is often followed by gradual diminution in vision, because of the increasing dystrophic changes in the cornea. This may eventuate in loss of all useful vision. While similar changes do occur after other operative procedures, most of the poor results I have seen have followed either removal of the lens or a discission. I might emphasize the importance of the utmost caution in severing secondary membranes in patients with advanced endothelial dystrophy. In many instances this simple operation is followed by rather rapid progressive opacification of the cornea. While such dire results do not always occur, they are sufficiently frequent to warrant serious consideration. Therefore when cornea guttata is present, it is my practice to defer any intraocular operation as long as possible.

QUESTION: Dr. Johnson, from what local appearance can the future course of opacities in the crystalline lens of the senile patient be determined?

DR. THOMAS H. JOHNSON: There are no local signs by which one can definitely predict the future course of lenticular opacities. However, certain changes can be seen with the slit lamp which are helpful. In the cuneiform opacities, in which radial spokes run axially in the anterior and posterior peripheral cortices, so commonly seen in elderly people, the course may be very slow provided the center of the lens is clear. Such opacities may exist as long as ten years without reducing the vision very much. In a case of nuclear cataract the slit lamp may show a golden glow in the nucleus of the lens before there is any reduction in vision. However, there is usually a definite reduction in the degree of hypermetropia or a pronounced shift to the myopic side. As the nucleus of the lens becomes more opaque, the golden appearance of the lens becomes more pronounced. The nuclear cataract may be present as long as ten years before incapacitating the patient, provided the anterior and posterior cortices remain relatively clear, as they may.

When the crystalline lens shows separation of the lamellas, myelin droplets and fluid fissures in the sutures and between the lamellas, the progress of the cataract may be expected to be rapid.

Posterior cortical cataract, which shows with the slit lamp as a saucer-shaped opacity in the posterior cortex, develops very slowly as a rule. As the opacity is near the nodal point, the vision is greatly interfered with, even in the early stages of development of the cataract. The rest of the lens may remain clear for many years. Fortunately, extraction by the intracapsular method need not be delayed overly long, as such a lens comes out very well.

The coronary cataract, which occurs at puberty, appears in the slit lamp as clubs and dots in a zone in the outer layers of the adult nucleus and the inner layers of the cortex and is nonprogressive. The opacities appear to be gray with the slit lamp and have a cerulean coloration with direct illumination. Later in life, the patient with these opacities may have senile cataracts.

QUESTION: Dr. Schlivek, what are the most recent theories to explain the progression of changes in field after a successful operation for the control of intraocular tension?

DR. KAUFMAN SCHLIVEK: After a successful operation, some eyes, despite careful watching, continue to lose the field of vision. It is generally thought that an increase in tension at intervals may account for the reduction of field. My own observation is that most of these eyes have vascular disease and that the picture of nutritional atrophy ensues.

In an article entitled "Glaucoma Without Hypertension," in Sorsby's "Modern Trends in Ophthalmology," A. J. Samoiloff stated the belief that the glaucomatous process is fundamentally due to an edema of the eye (particularly of the retina) which only in the later stages leads to degenerative changes, seen exclusively in glaucoma.

Magitot (*Ann. d'ocul.* **180:** 321, 1947) stated the opinion that glaucoma is a disease of the diencephalon characterized especially by vasomotor disturbances. These changes in the capillaries of the optic nerve result in atrophy.

QUESTION: Dr. Webster, what are the relative merits of the keratome section and the knife section in the operation for cataract?

DR. DAVID H. WEBSTER: They are of equal merit. Whichever one uses is a matter of personal choice, depending on the skill and confidence of the operator. For the occasional operator the keratome offers a safe approach, while the majority of busy surgeons prefer the knife. With respect to postoperative healing and resulting astigmatism, the courses are parallel.

QUESTION: Dr. Dunnington, what is your experience in the use of aureomycin (duomycin®) in cases of epidemic keratoconjunctivitis?

DR. JOHN H. DUNNINGTON: Duomycin® is a buffered sodium borate powder of aureomycin, which is dispensed in a 5 cc. vial. Distilled water is added to make a 0.1 per cent aqueous solution. This solution is administered in a dose of 1 drop every hour. Since the solution loses 98 per cent of its activity in twenty-four hours at body temperature, it must be kept in a refrigerator. At this lowered temperature the activity is reduced by only about 20 per cent. Because of its virucidal effect, Dr. Alson E. Braley, of our staff at the Institute of Ophthal-

mology, has used it in treatment of epidemic keratoconjunctivitis and dendritic keratitis. He has treated 51 patients with epidemic keratoconjunctivitis. As a result of this experience he feels that if it is used very early in the disease, before the appearance of the corneal infiltrates, it is most helpful. In 21 of the cases treatment was started very early in the disease, no appreciable corneal infiltrates developed and the process was over in about a week. In 30 cases it was used after the conjunctival symptoms had largely subsided and the corneal infiltrates were present. In this group no results were obtained. Therefore it would seem that to be of value the diagnosis must be made and treatment instituted in the initial stage of the disease. Of 10 cases of dendritic keratitis, hourly instillations of 0.1 per cent duomycin* resulted in prompt healing in 8, while no results were obtained in 2 cases. In the cases in which treatment was successful all staining areas disappeared in from twenty-four to seventy-two hours, and the process was completely cured in about a week. Our experience is still too limited to warrant any positive statements, but the initial results have been most encouraging.

QUESTION: Dr. Johnson, have you known of siderosis producing sympathetic ophthalmia?

DR. THOMAS H. JOHNSON: No.

DR. DAVID H. WEBSTER: About twenty years ago I recall having a patient with a traumatic cataract and advanced siderosis. Roentgenograms showed a foreign body in the lens, and inspection revealed a minute opacity in the center of the cornea. There was a foreign body, which I removed with the giant magnet, and then I removed the lens. Considerable soft lenticular matter remained. I saw the patient several weeks later, and his eye was quiescent. Eight or nine months later sympathetic ophthalmia developed in the other eye.

QUESTION: Dr. Schlivek, discuss your indications for operation on uncomplicated unilateral cataract.

DR. KAUFMAN SCHLIVEK: Generally it is preferred to defer operation on uncomplicated unilateral cataract. If the other eye is normal, operation may cause great discomfort. However, the cataract should be watched carefully, and as soon as signs of hypermaturity become apparent operation must be performed. If the patient has vision of 20/40 or less in the other eye, owing to corneal opacity or a lesion of the fundus, operation is indicated. When there are lesions in the fundus, one must be reasonably certain that the same condition is not present in the cataractous eye. In patients with alternating strabismus a unilateral mature cataract should be removed.

DR. JOHN H. DUNNINGTON: It seems to me that any question of this type must be an individual one; there are cases in which it is advisable to remove a unilateral cataract if the other eye is normal, but it should be the exception and not the rule. I personally have followed the rule that if a patient has a fluffy white cataract in the eye affected he is very likely to have subsequent trouble if the lens is left behind. If the condition is a sclerosed lens or a nuclear cataract, I am much more inclined to leave it alone.

QUESTION: Dr. Webster, what is the significance of the disconcerting flashes of light usually referred to the temporal field, a complaint which is

frequent among middle-aged and elderly patients whose media and fundi may show no coincident or subsequent changes?

DR. DAVID H. WEBSTER: These disconcerting flashes, known as scintillating scotoma, or scotoma fugax, are a manifestation of cerebral irritation. They may last only a few seconds or continue for half an hour. They may occur several times a day or weeks apart. The prolonged attacks beginning in the temporal field may extend over the entire field of vision, causing a terrifying temporary blindness. These severe attacks are usually followed by headache. They are of toxic or allergic origin supposedly from the intestinal tract—coffee and chocolate are the two commonest offenders. I have observed complete cessation of symptoms after appendectomy and cholecystectomy.

QUESTION: Dr. Dunnington, why is the anterior chamber deep in some cases of acute glaucoma with hypermature cataract, and what treatment is advised?

DR. JOHN H. DUNNINGTON: Secondary glaucoma as a complication of cataract arises either at the intumescent or at the hypermature stage. At the intumescent stage the rapid swelling of the lens produces acute narrow angle glaucoma, and this glaucoma is not the type under consideration. At the hypermature stage the lens is smaller than normal, so that with this loss of volume the anterior chamber becomes deeper. The rise in ocular tension associated with this type of cataract is therefore always accompanied with an anterior chamber of normal or greater than normal depth. The onset of the glaucoma is preceded by mild cyclitis. The angle of the anterior chamber is therefore blocked not by the forward displacement of the lens but by the increased protein content of the aqueous. Several factors have been mentioned to explain the development of the cyclitis, among which are (1) the toxic effect of the disintegrating lens material, (2) the irritation of the ciliary body through the movement of the loose nucleus of the lens and (3) spontaneous rupture of the capsule. It is probable that spontaneous dissolution of the posterior capsule occurs more frequently than is suspected. Should this take place, the sudden liberation of the toxic disintegrated lenticular material may precipitate a violent inflammatory reaction closely simulating endophthalmitis. In any event, the treatment which I have found most successful is removal of the lens. If possible, I extract it in capsule after using a retrobulbar injection to reduce the ocular tension, together with all the other safeguards now commonly employed. Paracentesis of the anterior chamber will bring about temporary relief and was formerly used as the initial procedure, but the eyes stand extraction so well that I now go ahead with the curative operation. If the ocular tension remains high after the retrobulbar injection, a small keratome incision is made and the anterior chamber is slowly evacuated before the section is completed with scissors.

QUESTION: Dr. Johnson, what is the earliest date at which you would remove an operable bilateral congenital cataract?

DR. THOMAS H. JOHNSON: The question of the earliest date that congenital cataract should be removed is a controversial one. Kirby expressed the opinion that if the opacities were allowed to obstruct light until the fourth year useful vision would not be obtained. Owens and Hughes reviewed the data on 231 eyes that had been operated on

and concluded that the results of operations performed before the age of 2½ years were not as good as those of operations done after that age. Cordes, in discussing the paper of Owens and Hughes, expressed the opinion that in the case of bilateral cataract one eye should be operated on at the age of 6 months and the fellow eye left until later. The character of the cataract should be the determining factor. To discuss those factors would require more time than is available. If I were to lay down a rule that would apply to all congenital cataracts, I should say operation should not be done before the age of 2 years.

DR. JOHN H. DUNNINGTON: I should not delay two years. If the cataract is complete and bilateral, I should favor operation within the first year. I prefer never to operate on the two eyes at the same time. If the operation on one eye goes well, I will proceed with the other after the healing is complete.

DR. KAUFMAN SCHLIVEK: If the cataract partially obstructs vision, and there is no fear of loss or suppression of vision, it is safe to wait two or four years; but when there is complete blocking of vision and the eye is healthy, operation should be performed before the age of 1 year.

QUESTION: Dr. Schlivek, what do you do for troublesome opacities in the vitreous unassociated with visible lesions?

DR. KAUFMAN SCHLIVEK: In cases of opacities in the vitreous one must make certain that there is really no pathologic condition. The pupil should be dilated and the eye studied carefully. If there is no lesion, the patient should be reassured and told that the opacities have no significance and often disappear. I generally prescribe ethylmorphine hydrochloride. Administration of iodides, nicotinic acid and calcium and subconjunctival injections have been suggested.

QUESTION: Dr. Webster, how do you best stimulate healing of an indolent ulcer of the cornea?

DR. DAVID H. WEBSTER: The most satisfactory stimulant for indolent ulcer is heat. I have tried phenol, dichloroacetic acid, trichloroacetic acid, iodine, actual cautery, moist chamber and iontophoresis and have concluded that dry heat is by far the most effective. To obtain the best results the application of heat should be continuous, at a temperature sufficient to reach the deeper structures of the cornea, yet below the lethal dose for living corneal cells; one of 115 to 120 F. meets these qualifications. I prefer the Shahan electric thermaphore, which is equipped with applicator tips of various sizes, so that one can select a tip approximating the area of the ulcer. This is held in light contact with the ulcer for forty to sixty seconds; atropine in oil is instilled, and both eyes are bandaged for forty-eight to seventy-two hours. It is important to immobilize both eyes after this procedure. Usually one application is sufficient.

DR. KAUFMAN SCHLIVEK: I think the new antibiotics have been a great help in the treatment of indolent ulcer of the cornea, and rarely do I find it necessary to cauterize an ulcer.

QUESTION: Dr. Dunnington, discuss partial keratectomy—its indications and results.

DR. JOHN H. DUNNINGTON: Partial keratectomy is indicated for removal of corneal opacities which do not invade the entire thickness

of this structure. If there is considerable vascularization of the opacity, the end results are not good. New-formed vessels invade the remaining stroma, and the resulting opacification is about as severe as was the original condition. This occurs either with or without postoperative irradiation. Furthermore, patients with vascularized opacity of the cornea have a stormy convalescence. The eye is very slow to heal, and until epithelization is complete it remains watery and extremely sensitive to light. My results have been so poor that I no longer advise this operation in cases of highly vascularized leukoma. In certain degenerative processes, such as band keratitis, the results are much better. The eye heals quickly, and considerable improvement in vision is often obtained. Its use in those types of dystrophy in which the pathologic process is chiefly confined to the superficial layers of the corneal stroma has been advocated, and good results have been reported. In view of the recent work on lamellar transplantation of the cornea, it is highly probable that this operation will supplant keratectomy as the procedure of choice in these conditions. These nonpenetrating grafts heal uneventfully, and the immediate results have been most encouraging. Sufficient time has not elapsed for a final appraisal of this procedure, but serious thought should be given to its use when one is considering a partial keratectomy.

QUESTION: Dr. Johnson, which miotics are essential?

DR. THOMAS H. JOHNSON: The miotics which are indispensable are pilocarpine and physostigmine. Pilocarpine produces few, if any, side effects. In early cases of chronic simple glaucoma as weak a concentration as a 0.5 per cent solution instilled morning and night may control the tension over a long period. As the solution becomes less effective, the strength can be increased up to 3 per cent and the solution instilled four times a day without any bad effect. The tendency of physostigmine to produce allergic conjunctivitis can often be overcome by dispensing the drug in a saturated solution of boric acid.

QUESTION: Dr. Schlivek, evaluate the new miotic drugs.

DR. KAUFMAN SCHLIVEK: The new miotics are neostigmine, methacholine, furfuryl trimethylammonium iodide (furmethide®), di-isopropyl fluorophosphate (DFP) and carbachol (U. S. P.). After the use of one of the newer miotics, it is often possible to return to pilocarpine or physostigmine and have much less reaction. For several years I have used the combination of methacholine chloride (mecholyl®), 10 per cent, and neostigmine bromide (ophthalmic solution), 5 per cent to great advantage. After pilocarpine and physostigmine produce a reaction, tension may be controlled with this combination for a long time. I have used furfuryl trimethylammonium iodide and carbachol in several cases but did not find them satisfactory.

Di-isopropyl fluorophosphate, according to the literature, is the most potent miotic. It produces prolonged miosis, ciliary spasm, false myopia and decrease of intraocular tension. It is generally prescribed in peanut oil. It does not produce conjunctivitis or dermatitis. In numerous reported cases this drug has succeeded where pilocarpine and physostigmine failed. However, it also fails in many cases and may not be harmless.

QUESTION: Dr. Webster, what is the present status of sulfonamide therapy in ophthalmic diseases (local and general)?

DR. DAVID H. WEBSTER: This is too comprehensive a question to answer in a few minutes. Except for the introduction of several new sulfonamide derivatives, there has been no change in sulfonamide therapy of which I am cognizant. E. L. Hughes reported good results in treatment of dendritic ulcer with local use of an ointment containing 6 per cent sulfacetimide three times a day and daily painting of the entire cornea with a 30 per cent solution (*Brit. J. Ophth.* **32:** 43 [Jan.] 1948). Clark reported that a 1 per cent solution of sulfamylon* (the hydrochloride of marfanil; 4-amino-2-methylbenzenesulfonamide) has a wide range of bacterial activity and is nonirritating and nontoxic. It is especially effective with Pseudomonas aeruginosa (ARCH. OPHTH. **38:** 682 [Nov.] 1947). E. Bruns pointed out that the treatment of ophthalmia neonatorum by the exclusive use of sulfonamides, which was successful during the early years, has become less and less effective lately; gonococci have become resistant to sulfonamides or only sulfonamide-resistant strains have survived. He recommended the additional use of penicillin (*Klin. Monatsbl. f. Augenh.* **112:** 327, 1947). The instillation every three hours of sulmefrin or 1 per cent sulfathiazole solution is effective in treatment of acute catarrhal conjunctivitis.

DR. KAUFMAN SCHLIVEK: The sulfonamides are very important drugs in many cases of infection of the uveal tract in which the focus is not known, and perhaps the only reason it is known that there is a focus is that the patient may have a rapid sedimentation rate. In these cases sulfonamides and penicillin have been valuable in treating a focus, even though one cannot put one's finger on it.

DR. JOHN H. DUNNINGTON: My results with treatment of uveal disease with sulfonamide and penicillin and any of the newer medicaments has not been as satisfactory as Dr. Schlivek's.

QUESTION: Dr. Dunnington, what is your surgical treatment of the retraction syndrome of Duane?

DR. JOHN H. DUNNINGTON: For the typical Duane syndrome no surgical treatment is advocated. A recession of the internal rectus muscle is not done in the presence of a convergence insufficiency. A resection of the fibrotic external rectus muscle increases the narrowing of the palpebral fissure without materially affecting the outward mobility of the eyeball. Transplantation of the lateral halves of the superior and inferior rectus muscles has been tried, but the results have not been satisfactory. In the atypical Duane syndrome a normal near point of convergence is not infrequently seen, and in some instances there is even actual esotropia in the primary position. When either of these conditions is present, a recession of the internal rectus does much for the patient. It decreases the narrowing of the palpebral fissure and removes the inward deviation in the primary position. It does not, however, increase the outward mobility of the eyeball. When one is doing a recession of the internal rectus in a case of the atypical Duane syndrome, it is wise, after thoroughly freeing the muscle, to suture it to the sclera 5 mm. posterior to its original attachment. Since in most cases it is possible to elicit diplopia by means of a red glass, one must be careful not to create a crossed diplopia in the field of action of the inter-

nal rectus, because such a result is much more annoying to the patient than the original condition. Caution is therefore the watchword in the surgical treatment of this syndrome.

QUESTION: Dr. Johnson, which approach do you prefer in exposing the inferior oblique muscle?

DR. THOMAS H. JOHNSON: I prefer the conjunctival approach. It gives better exposure, and the entire muscle is accessible. It is a further advantage that skin sutures can be avoided and there is no facial scar.

DR. JOHN H. DUNNINGTON: I cannot agree that it is easier to cut the inferior oblique at its origin through the conjunctiva, or that one gets a better exposure in this way. It is much easier to cut this muscle through the cutaneous incision, and one certainly gets a better exposure by this route, even though the operation can be done through the conjunctiva.

QUESTION: Dr. Schlivek, what method of sterilizing instruments do you employ in the office and in the operating room?

DR. KAUFMAN SCHLIVEK: Several years ago I investigated the method of sterilization of knives in some of the New York hospitals. It was quite uniform—in all of them the cutting instruments were placed in 70 per cent alcohol for twenty minutes. In the ophthalmologic service at Mount Sinai Hospital, the knives and keratomes are dipped in carbon tetrachloride for thirty seconds and wiped off with tissue and then placed in pure phenol for two minutes, followed by immersion in 95 per cent alcohol for thirty seconds. They are then placed in 70 per cent alcohol for twenty minutes. Just before use they are dipped in boiling water for fifteen seconds.

DR. DAVID H. WEBSTER: It seems to me that phenol dulls cataract knives and keratomes; I now use only alcohol and leave them for twenty minutes.

QUESTION: Dr. Webster, is rubella in a woman less than three months pregnant an indication for abortion?

DR. DAVID H. WEBSTER: During the past two years 3 patients with congenital bilateral cataracts associated with other anomalies have come under my office care. A history of rubella infection in the mother during the first months of pregnancy was present in 2 cases; in the third the mother had suffered a severe attack of influenza, which the family physician said was due to virus X. Of the 2 children with cataract, following measles, there were a congenital heart defect in 1 and unilateral microphthalmos in the other. The patient with cataract following virus X infection in the mother has mongolism. I wish to quote from an editorial in *The Journal of the American Medical Association* (October 30, 1948):

> Since Gregg and his associates presented original evidence that maternal rubella infection in early pregnancy appeared responsible for the frequent development of congenital anomalies in infants subsequently delivered, evidence for the truth of this influencing factor has grown rapidly. Anomalies most commonly noted have been ocular defects, deafness, heart lesions, microcephalus, mental retardation and dental defects. Estimates of percentage involvement of the fetus from maternal rubella during the first three months of pregnancy range from 90 per cent (Australia) to 27 per cent (United States), with a graded decreasing expected anomaly

rate from rubella infection in later pregnancy. Reports have been made of anomalous development following maternal infection in the eighth and ninth month of pregnancy. A woman contracting rubella during pregnancy has now approximately a ten to one chance of subsequently being delivered of a congenitally defective child.

Even with this conclusion, I agree with Dr. Lawrence T. Post, who stated in his discussion on Goar's paper on the relation of rubella in the mother to congenital cataract in the child (*Tr. Am. Ophth. Soc.* **43:** 135, 1945).

A practical question is whether abortion should be induced in mothers who have rubella in the first two months of pregnancy. I believe that this should not be advocated by the ophthalmologists, for the following reasons: (1) the diagnosis of rubella is not certain; (2) there have been cases in which normal children have been borne in spite of the rubella and this will continue to occur; (3) it is not rare that following an induced abortion there will be no subsequent pregnancy; (4) it is questionable whether there is good ethical background for inducing abortion in cases of this sort in which there is only the prospect that the mother may produce an abnormal child; . . . (5) the ophthalmologist would be counselling the performance of a questionable procedure by someone else, that person of necessity having to take the major share of the blame if the outcome was not as successful as was hoped.

Dr. Kaufman Schlivek: From my own experience with cases of cataract, mental retardation and congenital heart disease in children whose mothers had rubella during the first few months of pregnancy, I should answer, "Yes, operation should be done." The American Pediatrics Society and the National Society for the Prevention of Blindness have sent out a questionnaire in an effort to solve this problem. Until the results of that questionnaire are available, judgment should be withheld.

Question: Dr. Dunnington, how many prism diopters of change in a squint is effected by each millimeter of recession of the internal rectus, the external rectus and the inferior oblique muscles, respectively? And for each millimeter of resection of the same muscles?

Dr. John H. Dunnington: Many authors have answered this question. They have stated dogmatically that for each millimeter of resection or recession one may expect a definite amount of correction. With this view I am not in accord. Operations based on prismatic measurements alone are hit and miss affairs, for the amount of deviation present is only one of many factors to be considered in the preoperative analysis. It is not possible to enlarge on this theme here, but in passing one has only to mention the importance of visual acuity, refractive error and the near point of convergence and the fixing eye as preoperative factors which materially influence not only the choice of the operative procedure but also the amount of correction which will be obtained. Another difficulty encountered in trying to answer this question is the technic of measuring the exact amount of shortening or lengthening that is done. No two men will agree on the amount of resection a surgeon produces in an individual case. Is the measurement made while the muscle is stretched? If so, is the stretching maximal? Therefore what I estimate to be a 10 mm. resection some other surgeon will consider a 6 mm. shortening. Similarly, in recession the amount of tissue left on the globe varies

with the surgeon. Having therefore pointed out some of the difficulties of such rule-of-thumb operations, I shall in the most general terms state my impressions. One millimeter of recession of the internal rectus muscle will produce no appreciable effect, while 3 mm. of recession will correct on the average not more than 10 Δ of deviation unless there is a marked spasm of convergence, when the amount of correction may be as high as 25 Δ. If the same procedure should be carried out with a resection of the antagonistic external rectus muscle, the effect will be greatly enhanced. Similarly, 3 mm. of shortening of the external rectus muscle produces no appreciable change in prismatic measurements unless combined with a recession of the internal rectus muscle. On the other hand, a 10 mm. resection of the external rectus muscle mechanically limits the function of the internal rectus muscle even if it is done without touching the inner muscle. As a rule, a single 10 mm. resection of the external rectus muscle will produce about 15 to 20 Δ of effect, while if this resection is combined with a 3 mm. recession of the internal rectus muscle the usual result is about 40 Δ. In like manner, it can be said that a single recession of the external rectus muscle of 4 mm. corrects not more than 10 Δ of outward deviation, but if it is combined with a 6 mm. resection of the internal rectus muscle the amount of correction rises to 30 Δ or more.

In recession of the inferior oblique, the amount of correction obtained varies with the degree of overactivity of this muscle. If the opposite eye is habitually used for fixation, a 5 mm. recession corrects up to 25 Δ, but if fixation is maintained most of the time with the eye on which the operation is done the same amount of recession will produce much less effect. Judging from my experience, it is necessary to do a larger amount of recession of the inferior oblique muscle in order to offset a spasm of this muscle than is usually carried out on the horizontal muscles.

I regret my inability to give concrete answers to this question, but I have tried briefly to point out my reasons against the adoption of such arbitrary rules.

QUESTION: Dr. Hughes, do the results to date justify the extra expense and time involved in the fitting of mobile prostheses in the eye?

DR. WENDELL L. HUGHES: The only way to answer that question is to weigh the points in favor of the procedure against the points against it. In favor of the use of mobile protheses, one might mention particularly the fold in the upper lid; I think every one who has seen the integrated implant fitted with the integrated eye thinks that the fold in the upper lid matches the normal one more readily than in the case of the buried implant in the conventional type of enucleation; this is because the artificial eye is supported by the weight of the implant itself; with the integrated implant and the artificial eye, one can pull the lower lid down and the artificial eye stays there by virtue of the implant itself. Second, anyone will agree that the mobility with any type of integrated implant is much better than that with the conventional type of artificial eye. These are the two main points in favor of the new prosthesis; against it is the matter of the discharge; there is always more discharge from the integrated implant than from the completely buried implant. The question of expense to the patient is a much more difficult one, and

the fitting of the artificial eye is somewhat harder and requires more skill on the part of the maker of the artificial eyes. It is not so difficult as some of the makers of artificial eyes would have one believe. A stock eye can be used in the majority of cases, but occasionally a custom eye is necessary for the best results. However, a stock eye with a peg on the back should not cost much more than the ordinary artificial eye. I realize that there has been difficulty in getting plastic eyes of any kind made at a reasonable price, but this situation will correct itself in the near future, I am sure.

The question of late extrusion and other complications that may occur with the integrated implant must be taken into account. It is not always possible to get sufficient tissue, muscle and fascia to hold the eye permanently in place, and some of them do come out. Nothing is lost permanently if the integrated implant is extruded, since the buried implant can be put in at any time afterward. All work on implants is necessarily in the experimental stage, and patients should be informed that no mobile implant has been in place more than four years and that it will take at least ten years before final results will be known and the work being done can be judged. A great deal of work is being done, and just what will come of it eventually no one is in a position to say.

QUESTION: Dr Schlivek, what are the ophthalmoscopic indications and contraindications to thoracolumbar sympathectomy?

DR. KAUFMAN SCHLIVEK: Keith and Wagener's classification of changes in the fundus into four groups is generally accepted. With changes in the first and second groups, operation is indicated as soon as signs of progression of the hypertensive disease appear; with changes in the third group, many patients, after the general physical conditions have been studied, may be operated on and do well. With changes in the fourth group, the procedure is frequently contraindicated; but if the retinal vessels do not show advanced sclerosis sympathectomy should be done, and the prognosis is not bad.

The ophthalmoscopic contraindication to sympathectomy is extensive sclerosis of the retinal vessels. More important contraindications than the ophthalmoscopic signs are impaired renal function, cerebral accident, cardiac enlargement and diabetes.

QUESTION: Dr. Webster, what do you consider the best operative procedure in chronic (wide angle) glaucoma?

DR. DAVID H. WEBSTER: For chronic glaucoma, which a decade ago was known as compensated glaucoma, and is now designated as wide angle glaucoma, many operative procedures have been advocated. The two I use most frequently, and find the most satisfactory, are the Elliot trephination and iridencleisis. Either operation, without undue trauma, will control tension in the majority of cases. Some glaucomatous eyes do not tolerate any form of surgical intervention. The question is what is the best operative procedure. To answer that dogmatically, one would have to discard the various factors entering into the choice of operation, such as width of the palpebral fissure and prominence of the globe, the patient's occupation, climate, friability of the conjunctiva and racial characteristics. In persons with prominent globe or wide palpebral fissure, especially those whose occupation exposes them to the bright light of the seashore or the tropics, the glare following an iridencleisis

is a formidable handicap. An Elliot operation with peripheral iridotomy is the proper procedure. In negroid patients, in whom keloids are prone to form, the Elliot trephining is a poor procedure, while iridencleisis is far more satisfactory. In patients with long-standing glaucoma and a very friable conjunctiva, the bleb following an Elliot trephining is so tenuous that subnormal tension is the rule, and this is disastrous. Such patients do better with iridencleisis. The procedure I follow most frequently is an Elliot trephination, using a 1.5 mm. blade, and a peripheral iridotomy.

Wendell L. Hughes, M.D., *Chairman*

Isadore Givner, M.D., *Secretary*

Dec. 20, 1948

REPORT OF CASES

A Magnetic Implant. Dr. Richard C. Trautman (by invitation).

Experiences at the New York Hospital with a new type of integrated implant were presented. The principle involved, as differentiated from the pin type of implant, is the absence of any mechanical connection of the implant and the prosthetic appliance. The integration is accomplished, rather, by means of a magnetic field between the implant and the prosthesis. This makes it possible to cover the implant completely and does away with infection and late extrusion, which are sometimes encountered with the present types of exposed, pin-integrated implants. The implant used is of a new plastic, a polyethylene glycol, a wax of high molecular weight, which has been demonstrated to produce no reaction in the tissues. This encloses an "alnico" magnet, which is pear shaped and flattened anteriorly where the poles of the magnet present. The neck of the implant, to which the muscles are attached, is countersunk and contains a double band, 3 mm. in width, of tantalum mesh. The implants are 18 and 16 mm. in diameter, respectively. The technic of the operation is simplified in that the rectus muscles are mattressed to a black silk band, which is merely tightened and tied about the neck of the implant. Tenon's capsule is doubly mattressed over the face of the implant, and the conjunctiva is closed with a running silk suture. The report is based on experience in 13 cases, the first implantation being performed on May 17, 1948. There have been no extrusions. One implant became uncovered after operation, owing to the use of a purse-string closure of Tenon's capsule. This implant has retained full motion.

The shells in use have been designed and made by Mr. Leon Morrell. Their motion is full and satisfactory. Acknowledgment of help in manufacture of the implant, information about and material furnished for the magnets is made to the American Cystoscope Makers, Incorporated, and to the Indiana Steel Products Corporation.

Two slides picturing the implant and prosthesis and a four minute film of the postoperative results were shown.

DISCUSSION

Dr. Chester A. Weed: For over six months at the Manhattan Eye, Ear and Throat Hospital, we have been working experimentally on a similar magnetic type of implant, but have not progressed so rapidly

or so far as Dr. Trautman. On Dec. 9, 1948 we used this implant clinically in one case. The results to date are promising.

The magnetic implant measures 17 by 15 mm. and weighs 4.5 Gm. Two holes, 5 mm. in diameter, passed through the diameter of the implant are arranged perpendicularly to each other. The rectus muscles are drawn through the holes by means of chromic surgical gut sutures, and each muscle is sutured to the opposite rectus muscle in a manner similar to the procedure used in the Guyton implant.

PAPERS OF THE EVENING

Production and Detection of Radioactive Isotopes for Medical Research. SERGE A. KORFF (by invitation).

Atomic nuclei are composed of protons (charged) and neutrons (uncharged). Each chemical element has a characteristic number of protons and one or more characteristic numbers of neutrons, each different number corresponding to a different isotope of that element. Rearrangement of the number of internal particles usually increases the internal energy of the system, and this, in turn, usually manifests itself by the nucleus' becoming radioactive. The usual method of making a nucleus radioactive is by neutron bombardment.

Neutrons may be obtained in great quantity in the large chain-reacting piles at such places as Oak Ridge. They may also be produced by various types of accelerating machines, such as the cyclotron. In these machines, protons, in the form of hydrogen nuclei, are speeded up and then allowed to strike a target composed of any material, such as lithium, beryllium or heavy water, in which the neutrons are loosely bound. The neutrons are thus detached from the nucleus, slowed down by passage through a moderator and then allowed to be absorbed by the element to be activated.

Detection of radioactivity is accomplished by any device capable of detecting or measuring ionization. This includes Geiger counters, proportional counters, ionization chambers, cloud chambers and photographic emulsions. Counters are the devices most frequently used in medical research at present, because of their versatility. Many differing sizes and shapes may be used, depending on the particular problem encountered. Counters, especially the proportional counters, can be adapted to have preferential sensitivities for particular particles. For example, alpha rays can be counted to the exclusion of a much larger number of beta and gamma rays, or beta rays can be detected and distinguished from a background of scattered roentgen rays. Special geometric designs can be used, and the active specimen introduced inside the counter, or reversely the counter may be placed inside the specimen.

Uses of Radioactive Isotopes in Medical Research. DR. EDITH H. QUIMBY (by invitation).

In medicine, radioactive isotopes of common elements have been used in two broad fields, tracer studies and therapy. Atoms of these isotopes are chemically and biologically inseparable from ordinary atoms of the same element. By virtue of their radiations, they can be detected in extremely small amounts; hence, a minute quantity of a radioactive isotope may be used to label a considerable amount of material. Its

course through the body can then be traced—uptake, distribution, transformation into different compounds, deposition or elimination. Valuable diagnostic technics have been developed from such studies. Elements of particular interest are sodium, phosphorus, iodine and iron.

In order to employ these substances in therapy, it is necessary to determine whether the material in question can be made to concentrate in the diseased organs or tissues and deliver sufficient radiation there without unduly harming the rest of the organism. This implies a knowledge of the radiosensitivity of the lesion and a study of the distribution of the isotope within the body. In general, it can be said that up to the present the therapeutic developments of isotope research are disappointing. (The uses of iodine and phosphorus in treatment of thyroid disorders and leukemia, respectively, were discussed.)

The matter of protection of everyone concerned with radioactive isotopes is extremely important. Unless due care is exercised, local and systemic damage can result from handling these materials, even in the small quantities necessary for tracer work.

Radioactive Isotopes in Ophthalmology. DR. LUDWIG VON SALLMANN.

In the last seven years artificial radioactive elements have been used to study certain phases of physiologic fluid exchange in the eye. Kinsey and co-workers laid the groundwork in excellent investigations. These authors were followed by Visscher and Carr; Wilde, Scholz and Cowie, and Wang. The main results, based mostly on the work of the Howe Laboratory, are summarized: The apparent rate of entrance from the blood into the aqueous humor is rapid for Na^{24} and Cl^{38} but slow for P^{32}. The rate of formation of whole aqueous is comparable to the rate of entry of these radioactive tracers, whereas the movement of water is about ten times as rapid. $Sodium^{24}$ enters the aqueous from the blood at about twice its speed in moving into the spinal fluid. Kinsey and Grant arrive by mathematical formulation and integration of their experimental results at the opinion that the monovalent electrolytes tested are transported into the anterior chamber as a result of a secretory process. In all these studies the quantities of the radioactive material were measured in Müller-Geiger counters on samples of fluids withdrawn from the eye, cerebrospinal fluid and blood.

With this technic it was not possible to obtain information on the topographic relation of the tracer atoms within individual structures of the eye. This problem has been investigated in the last two years in the Knapp Laboratory, partly in cooperation with the Department of Radiological Research, College of Physicians and Surgeons, by modifying or designing autoradiographic technics for the eye. A new gross method for 2.5 mm. frozen slices and the microscopic method of Evans for thin paraffin sections were employed. Na^{24}, P^{32} and I^{131} were used in rabbits and, in a few instances, in cats, dogs and monkeys. The movement of the radioactive element from the blood into the fluid and structures of the eye and their diffusion gradient within the eye were made visible on the photographic film; that is, concentration differences of the radiating atoms showed up in the shades of blackening of the radiosensitive emulsions. The regions of the ciliary body and of the optic nerve were the main portals of entry. Ultrafiltration through the capillaries was suggested to be the predominant factor in the passage

of the tracers from the blood to the ocular fluids. The autoradiograms demonstrated the difference of relative permeability of the ciliary capillaries and that of other capillary beds in the eye in various species of experimental animals. Na^{24} and P^{32} gave similar autoradiograms. I^{131} did not enter readily the ocular fluids but remained concentrated in the cornea, sclera and iris. Densitometric readings of the autoradiograms open the way for quantitative estimation of the results. Comparative studies with roentgen radiation ruled out the possibility of unphysiologic effects of the radiation emitted from the tracers when these substances were applied systemically in the dose used. This was not the case, however, in intravitreal administration of Na^{24} in studies on absorption from the vitreous.

DISCUSSION

DR. CONRAD BERENS: A patient aged 66, who was to have an enucleation for sarcoma of the choroid, was given 174.7 microcuries of radioactive sodium intravenously. This was done in conjunction with Dr. Joseph H. Krug and Dr. Beverly C. Smith. Three-tenths cubic centimeter of aqueous and 0.5 cc. of vitreous were removed three hours after the injection, immediately after the enucleation.

DR. BEVERLY C. SMITH: The results in the aspirated material showed 0.00963 microcurie of sodium per cubic centimeter of aqueous and 0.00361 microcurie of sodium per cubic centimeter of vitreous. In the blood serum 0.00918 microcurie of sodium per cubic centimeter was found. The close similarity in content of sodium of the blood serum and of the aqueous was noted.

DR. LUDWIG VON SALLMANN: The figures are similar to those given for animals. Three hours after injection the sodium contents of the plasma and aqueous are quite similar. No other figures on sodium in the vitreous are available for comparison.

Wendell L. Hughes, M.D., *Chairman*

Isadore Givner, M.D., *Secretary*

Jan. 17, 1949

PRESENTATION

Speed Light Photography in Ophthalmology. DR. A. BENEDICT RIZZUTI (by invitation).

Speed light photography affords the use of a new technic in photographing the external eye. The essential feature consists of an electric flash tube, developed by Mr. H. E. Edgerton. This new type of illumination is extremely brilliant (about 12,000,000 lumens) and of very short duration (0.0001 second) and produces no discomfort. From a single tube 10,000 or more light flashes can be obtained. There is no appreciable sense of heat to the patient, even when the light is placed as close as 4 inches (10 cm.) from the eye. The tube is flashed by means of a power pack, which operates on the usual alternating house current.

Photography of the external eye presents special problems, chief of which are (1) lid reflexes, (2) constant motion of the eyeball, (3)

limited tolerance of the eye to prolonged strong illumination, (4) annoying corneal reflections, (5) convexity of the eyeball, making it difficult to obtain a sharp picture on a flat film and (6) annoying shadows produced by the eyebrow, the overhanging orbital edge and the upper cilia.

In order to overcome most of these difficulties, a photographic unit was assembled, which consisted mainly of a 2¼ by 3¼ inch "speed-graphic" camera, to which was attached an electric flash tube, both being mounted on a sturdy metal base. The shutter of the camera was synchronized with the light, which was placed about 4 inches from the eye. Critical focusing was obtained by means of the ground glass behind the camera. Color or black and white film was used with the shutter diaphragm opening set at f.8 and f.32, respectively. By means of special film adapters, four 35 mm. pictures could be obtained from one 2¼ by 3¼ inch negative.

The technic was standardized so that the operation of the photographic unit became almost automatic. It was possible to "freeze" all types of motion of the eye at this high speed. The corneal reflections were minimized, and excellent depth of focus was obtained. The light source was well balanced for color photography, and the same tube could be used repeatedly, thereby greatly reducing the cost of operation. Excellent black and white photographic enlargements of the limbal vessels, aqueous veins and details of the iris to a magnification of 35 were made possible by this method.

With this new technic excellent photographs are obtained, and new avenues of photographic investigation in ophthalmology are opened.

DISCUSSION

DR. SAMUEL GARTNER: The camera made by Fairchild which I have been using is more complicated; when the button is pressed, the focusing light goes out, the diaphragm is shut down, the shutter is released and the next film is wound into place. This complication, though adding to the usefulness of the camera, increases its cost. Dr. Rizzuti's camera has the essentials, and with the speed light it is the best means of photographing the eye.

PAPERS OF THE EVENING

Clinical Aspects of Aniseikonia. DR. JOHN P. MACNIE.

The questions whether there is such a thing as aniseikonia, whether it can be measured and whether its correction is of any benefit were raised. Powerless lenses with parallel surfaces which magnify or minify images can be manufactured, and the same effect can be included and is an incidental factor in ordinary ophthalmic lenses. With good corrected vision in the presence of monocular aphakia, aniseikonia of about 25 per cent is encountered. Measurements of aniseikonia can be made and reproduced and the results of various methods correlated.

The records of over 1,000 patients were reviewed from five to ten years after examination. From this study it was concluded that psychologic disturbances, refractive error, anisometropia and muscular imbalance were not factors in the aniseikonia and that iseikonic corrections could be of value for the patients who had not benefited from the usual ophthalmologic measures and whose symptoms were associated with use of the eyes, although no characteristic symptoms were indicative of

the presence of aniseikonia. It is felt that of any such patients for whom iseikonic corrections are tried, approximately one third will receive no benefit, one third will be improved and one third will be relieved of all, or most, of their symptoms.

Lighting from the Standpoint of the Illuminating Engineer. Mr. C. L. Crouch (by invitation).

The illuminating engineer has made good progress toward an appreciation of the relation of the physical end product of lighting to human needs. He has come to realize that his service to man must be based on a sound understanding of the psychologic and physiologic relations of light and vision. He has organized the members of his profession into groups, who, in sequence, will gather, interpret and apply current knowledge and experimental data. He has formed an auxiliary group to administer a research fund in sponsoring experimental investigations into the unexplored phases, as well as to reexamine some of the previous work on which the technics of application of lighting are now based.

A recapitulation of the present relation between light and vision was given, and these relations were interpreted and applied to a typical field of school lighting. Other fields, such as the lighting of homes, offices and commercial and industrial locations, were treated in like manner.

Effects of New Light Sources On Human Vision. Mr. Samuel G. Hibben (by invitation).

Some of the new illuminants, as well as many of the changing habits of men, have placed extremely heavy tasks on the eyes. Quantitatively, man's eyes are not generally subjected today to any wider ranges of object brightnesses than were known to his ancient ancestors, namely, from about 10,000 foot candles of noon sunlight to 0.02 foot candle of moonlight, or perhaps to 0.0002 foot candle of starlight. However, his indoor seeing tasks rather generally are performed amidst a wide, and sometimes constantly changing, variety of brightnesses of background or of task, and for prolonged periods. A multiplicity of low-hung, bare lamp bulbs, glass desk tops, specular instruments and glistening black machines adds its burden to vision.

Qualitatively, light may indeed have widened the boundaries of its wavelengths, so that, in addition to merely one octave, known as the visible spectrum (roughly from 8,000 to 4,000 angstrom units), one now frequently interprets "light" to include the octave of longer wavelengths, namely, the near infra-red region of 16,000 angstrom units or longer, and, more particularly, the octave of ultraviolet rays, extending to about 2,000 angstrom units. Thus, in addition to normal light sources, there are infra-red and heat lamps and several varieties of ultraviolet lamps. More than 1,500,000 sun lamps and sterilization lamps are in use in this country, and the number increases.

Physiologically, the human eye, given sufficient time, could adapt itself to many slowly changing conditions. Present day light sources and their uses have developed within only the last two or three decades. One obviously must depend on sensible practice and intelligent application rather than on nature's slower evolutionary means of protection.

Preliminary to any survey of the relationship of vision to the characteristics of light sources, one may well review some features of the adaptability and sensitivity that characterize the human eye.

1. Infinitesimally small amounts of energy are sufficient for some types of vision. In 1889, Dr. Langley, in determining how much energy is needed at the retina to produce sensation in the cortex, stated that perhaps it was on the order of three-billionth erg. (To lift 1 Gm. a distance of 1 cm. requires 1,000 ergs.) This would mean about 1,000 quanta of light, or that volume of luminous energy which would be required to change 1,000 molecules of retinal material. Later researches (Hecht) have reduced this figure to 50 to 150 quanta. Even though sometimes more than one-half the energy impinging on the cornea is absorbed before reaching the retina, and though this absorption within the eyeball differs tremendously, depending on the wavelength of the incoming energy, nevertheless, in all cases the threshold of human vision is surprisingly low. But this is the energy required to see light, not to see with it.

2. At approximately 20 degrees from the central axis, after about three quarters of an hour of dark adaptation, the scotopic vision may be one thousand fold more sensitive than that under what might be termed normal illumination. This ability is involved in the selection of subjects for certain seeing tasks, or sometimes when sudden changes of brightness may involve temporary blindness and resultant accidents.

3. The speed of vision is occasionally a factor. Perhaps a flash of light for one-thousandth second is amply sufficient for the visual sensation, but below about one-fifth second the effect on the retina is a time-intensity product. Everyone has experienced a flash of tremendous brilliance, but one the duration of which is so short that there is no feeling of discomfort. Some of the present day "photoflash" and discharge lamps, used in photography and as well in aviation and signaling, involve these factors. But aside from retinal fatigue, "snapshot" pictures of the eye require ample target brightness, and the slow, "time exposure" pictures of the eye under dim illumination are synonymous with slow action.

4. Visual acuity is a variable. On the retina the rods may be approximately 150,000 to the square millimeter and the number of cones in the fovea may be of the order of 6.5×10^6. Naturally, one limit of vision is set by the smallness of a retinal image, which presumably should cover an area filled by a fair number of nerve fibers. With an increase of contrast brightness (and minimized glare) one can see smaller objects, but not indefinitely. Generally, however, in lighting practice illumination is far below optimum values.

5. At extreme ranges of brightness the eye is unable to judge accurately the color of the target. Dark objects when illuminated to very high brightnesses will appear to fade from dark toward light shades, and even a black object can be made to look almost white if powerfully illuminated. It is a common experience also to encounter vision under conditions of dim street lighting or on a moonlit night, when at a brightness somewhere between 0.01 and 0.001 foot lambert there is a shift from cone to rod vision accompanied with inability to perceive color. However, normal illumination rather infrequently involves these

extremes. Special lighting must be planned for the airplane pilot, for the deep-sea diver, for the night motorist, for all who at extreme ranges of brightness may depend on color judgment.

Many other known facts about the human eye could be useful in appraising its reaction to modern illuminants and practices. However, it will suffice to note some pertinent characteristics of present day light sources as these may influence visual comfort.

1. Modern illuminants, particularly fluorescent lamps, are available in almost all the rainbow colors of the spectrum. Under equal brightnesses and similar surrounding conditions, the color of the light makes little or no difference to the eye, when its range is not too widely different from the so-called white daylight. However, psychologic influences appear, and of course background contrasts may involve many peculiarities, and sometimes peculiar distortions. Briefly, the illuminating engineer starts by choosing that tint of light which makes the object appear just as one's memory tells him it ought to appear.

2. The well nigh invisible flicker of some modern illuminants has on occasion been viewed with alarm, and yet there seems no good evidence of permanent harm to the eye from this inherent characteristic. The fluorescent lamp does vary in luminous output at twice the frequency of the alternating current. This stroboscopic effect, however, is not viewed as detrimental, for a pair of fluorescent lamps can be electrically staggered so as to smooth out the peaks and valleys; the slow action of the fluorescent lamp phosphor will reduce the luminous drop, and in other ways the flicker of a well designed fluorescent installation can be much less than the flicker of many of the incandescent installations that have for many years operated on, say, 25 cycle frequency.

3. The modern fluorescent illuminants generally are less bright intrinsically (in terms of foot candles per square inch) than some of the lamps of a decade or more ago. This trend is in the right direction, but there is a caution here, namely, that one must not reduce one's efforts to shield and shade those illuminants which are constantly in the field of view, even though unshielded they might be tolerated.

4. Among the new sources will be found those which emit long wave ultraviolet rays for biologic and erythemal results, as well as other sources radiating short wave ultraviolet rays for bactericidal purposes. Both these qualities of "light" call for superior intelligence in the planning of a complete interior lighting installation. Both classes of lamps are sharp tools, but are safe in the hands of the expert. Both may, in the near future, be found to form an increasing percentage of the regular lighting lamps.

5. Since modern illuminants tend to emit increasingly larger volumes of light, perhaps the greatest hazard is glare—the irritation from the bare, unshielded bulb! Since this fault seems the easiest to remedy, one might well begin to caution against glare as an elemental improvement.

One may conclude, therefore, that even though today's light sources are increasing in variety, they generally do not in themselves impose too difficult a burden on the human eye. Rather the reverse—they make it easier for the intelligent achievement of those well designed lighting installations that should lead to more comfortable vision.

DISCUSSION

DR. LEGRAND H. HARDY: Mr. Crouch has admirably outlined the engineering point of view on illumination and has given us the program of the Illuminating Engineering Society. It is gratifying to feel that, owing largely to his activities, the society is developing into a scientific organization of engineers. Mr. Hibben has informed us of recent developments in the production of new light sources. Both speakers hold out great promises for improving both the pleasantness of one's surroundings and one's ocular efficiency.

Our chairman has asked me to bring the discussion to specific practical considerations which can be utilized by the members of this Section.

The questions we are most frequently asked are these: 1. What kind of light shall I use? 2. How much light do I need?

Neither question can be answered categorically. The first question usually means: Shall I use fluorescent lighting or incandescent lighting? The answer will depend on esthetic considerations, technical considerations and the extent of the area to be illuminated. Esthetic considerations usually lead away from fluorescent lighting in eating places—particularly small or private dining rooms, where the habit of viewing prepared food under incandescent illumination of low color temperature is strongly intrenched. With the development of new fluorescent tubes, the objections to this form of lighting will probably be overcome. Technical considerations lead strongly away from fluorescent lighting in situations where fine color discriminations are to be made. Here, except under special conditions, a modified incandescent light, technically known as ICI-C, should be used. Its use is mandatory for successful color vision testing. The area to be illuminated likewise exerts influence on the decision. It is usually simpler, more economical and more efficient to use small incandescent units to increase the local illumination on a small area. To get a general high level of illumination over a large area, the use of fluorescent lighting is practically essential. It is generally considered inadvisable, largely on esthetic grounds, to mix the two. Most of the dissatisfaction that comes from using either type of illumination arises from poor distribution, such as glare, high fixture brightness, high brightness differences, poor diffusion and unshielded sources.

The second question, "How much light do I need?," could, for the purposes of this discussion, better be stated, "How much light should I have?" Here a wide divergence of opinion is apparent. One group, often called "commercial salesmen," whose dependence on the lighting industry, directly or indirectly, leaves them open to the charge of meretricious motivation, argues for relatively high levels of illumination, 50, 100, 400, 500 or even 1,000, foot candles. Another group, sometimes derogatively described as "old fogies," "reactionaries" or "horse and buggy doctors," argues that such high levels are neither necessary nor helpful. As with "socialized medicine," a strong case with impressive statistics can be made out for either side. I find myself in the second group, with a definite feeling that intensity levels equal to, or, in most cases, less than, those recommended by the committee of the Illuminating Engineering Society are fully adequate for all ocular work, and that it would not be economic, desirable, or even justifiable, to increase them. The argument that the human eye functions well under outside natural

conditions of high intensity levels can be answered with the statement that it functions just as well inside with only a small fraction of the outside intensity, and that to achieve a duplication of external conditions in small spaces is extremely difficult.

A major factor in frustrating us in our attempt to acquire objective evaluations has been the lack of general criteria. Eyestrain, as an example, is neither accurately definable nor objectively (or operationally) measurable. Many quantitative tests for eyestrain have been devised, but none, so far, has achieved universal acceptance. New methods for objectively evaluating fatigue and physiologic effects due to changes in lighting promise to put these studies on a much firmer basis. Determination of flicker fusion, action currents and ballistographic and neuromuscular tension are among such methods.

There can be no question that in the laboratory and in industry modification of illumination has produced measurable and significant results. Output on a given job has been increased by raising the local brightness level alone; the accident rate has been lowered; the psychologic effect on workers has been noted and evaluated. In the laboratory, where other factors were presumably controlled, the speed of discrimination, the visual acuity and the detail discrimination have been charted. It is extremely difficult to make a test situation identical with a working situation; but out of these experiments the factors that constitute good lighting are becoming apparent, and with their appearance, recognition and evaluation better lighting must follow.

For the oculist interested in acquiring further knowledge in this field, I would recommend the publications containing the committee reports and the "Lighting Handbook" of the Illuminating Engineering Society. The "calculux" (the small circular intensity level indicator demonstrated by Mr. Crouch) may be obtained through the Holophane Company, 342 Madison Avenue, New York.

MR. GEORGE AINSWORTH (by invitation): What is the one underlying factor which is bound to make artificial lighting useful and economical? Mr. Crouch showed us two Snellen test charts—one clean; the other smeared over with a thin coat of white paint, imitating and duplicating reflected glare. These illustrate what Dr. Ferree and Dr. Rand discovered twenty-five years ago in their optics laboratory at Johns Hopkins University. The entire ceiling of this laboratory was a glass skylight. They could let in the exact amount of daylight which would duplicate levels within the reach of incandescent lighting. This gradation and quantity were carefully achieved by two or three series of sliding translucent curtains. Many tests were evolved and used daily with a series of subjects until a final and unequivocal conclusion was reached, namely, that only diffusely reflected light can form a clear image on the retina. Specular reflected light is entirely wasted or tends to blur and confuse the image. They found that, regardless of the intensity of light, if rays were reflected at any angle that proceeded back to the eye, the visual effect was the equivalent of the Snellen chart smeared with a thin coat of white paint. The greater the intensity of light, the poorer the visibility. The reflected beams of light, like the white paint, tend to make the black letters disappear into the white background. The desirable black and white contrast which makes printing clear and visible is so

reduced that the words and letters are no longer visible. Is there any simple and easy way in which the layman can quickly determine whether a sample lighting demonstration is likely to prove satisfactory? He can be sure that the image cannot be blurred if there is no evidence of definite shadow below a pencil held 2 or 3 inches above and parallel to white paper laid on the desk. If there is a shadow, there certainly is an objectionable light source in the overhead. In daylight, shadows occur only when the sun shines, in which situation the retina and the iris under control of the autonomic reflex are dulled and the sensitivity is so reduced that there, naturally, are no objections to daylight at such intensities. (Artificial lighting reaches only meager levels equal to about one hundredth of low sunlight levels.) Nature's system of conditioning the sensitivity of the eye to conform exactly to the quantity of photons that pass through the iris is called adaptation.

When an artificial lighting situation presents a combination of brightnesses which is beyond any experience of the eye during its evolution at an equal daylight level, the mechanism is unable to adapt precisely for the perfect resolution of the visual problem presented. When man departs from nature's norms, his faculties degenerate. An unnatural interior lighting situation induces an artificial neurosis. Professor Maier, of the University of Michigan, has pointed out that disorganized behavior and frustration follow when an artificial environment places demands on the human organism which, by evolution under natural conditions, it is incapable of handling. Animals experience conflicts and emotional disorders when confined under adverse and unnatural conditions with which their inherited stabilization mechanism cannot cope. People and animals become resentful, irritable and aggressive under an undeserved punishment. When an incipient visual defect or abnormality is already present, a catastrophic reaction is initiated. Thus, frustrating and unnatural lighting conditions are bound to reflect adversely in the person's life and activities outside the irritating situation caused by the problem that could not be solved by the voluntary or involuntary nervous system.

Those high public officials in charge of the well-being of office workers of the nation in post offices, courthouses and tax bureaus from coast to coast have come to a decision on artificial lighting that corresponds with the findings of Dr. Ferree and Dr. Rand over a quarter of a century ago. Complaints from office workers, draftsmen, engineers and accountants have been eliminated only when all direct beams of light from the overhead were also eliminated. The illumination must be entirely diffuse. I call it spatial brightness equilibrium. The new Government specification calls for a uniform light source in the overhead emitting at the rate of approximately 150 lumens per square foot of area. I have no hesitation in stating that this specification will provide the best solution to the problem of artificial lighting, now that there are available the wide series of color temperatures and spectral qualities so cleverly demonstrated by Mr. Samuel Hibben. The new fluorescent tubes providing long lines of uniform emission over wide areas can be used in a revolutionary lighting fixture, so that their primary emission of 2,000 units per unit area can be reduced to a rate of 150 units over all the units of the area. The new Government design simulates at this rate the luminous continuum of the natural sky when daylight is most delightful and causes no eyestrain or irritations when one is reading, writing or drafting for long periods.

Each one of us can prove the truth of these conclusions by reading outdoors on any fine day shortly before sunset or at many other times when clouds obscure the sun.

Notwithstanding the defeatist attitude discouraging the duplication of natural light, as set forth by illuminating engineers in their new "Standard Lighting Guide," I am willing to take the dogmatic stand that the United States Government authorities are entirely right in eliminating all primary and direct lighting beams and in reducing the emission to a rate of 150 units or less. My forty-five years of experience in lighting compels me to disagree totally with the effort of the Illuminating Engineering Society to promote lighting ideas according to which it is considered undesirable to duplicate natural lighting at any level, distribution or spectral quality. A more careful statement of this thesis will appear in the February issue of the *Journal of the Franklin Institute*, in a paper on illuminating engineering and the correlation of room colors, by Prof. Parry Moon, of the Massachusetts Institute of Technology, and Dr. Domina Eberle Spencer, of Brown University.

Dr. James W. Smith: In 1924 I had the privilege of addressing the convention of the Illuminating Engineering Society on a four year survey made at the Electrical Testing Laboratories (Macdonald, N. D., and Smith, J. W.: Periodic Eye Examinations in a Testing Laboratory, *Tr. Illum. Engineer. Soc.* **20**: 168-182 [Feb.] 1925). It would be well to emphasize again that normal eyesight is essential to the qualification of a worker for his tasks; otherwise, he will not benefit from the good illumination devised by the illuminating engineer.

When our investigation began, 59 per cent of the employees were laboring under the handicap of an ocular or visual defect. We established standards that barred from critical work applicants with (*a*) subnormal vision not correctable with eyeglasses, (*b*) accommodative power greatly below normal, (*c*) intraocular disorders and (*d*) incoordinate action of ocular muscles. When the abnormalities were treated, we observed that the photometrists and the employees engaged in testing the lighting of incandescent lamps (exposed to about 2,000 lamps, emitting from 30 to 20,000 lumens each) suffered no greater eyestrain than those engaged in routine office procedures.

Dr. Joseph Irving Pascal (by invitation): Experiments conducted on visual fatigue resulting from visual tasks under different conditions, some of them conducted in connection with a study of reading difficulties and reading disabilities, have shown that one of the most important factors in causing fatigue from a visual task is the motivation behind the task. When such motivation is strong, a visual task, even under adverse conditions of lighting, will produce less fatigue and less difficulty than a visual task which has slight motivation under optimum conditions of lighting. Motivation is a human element; it is a psychic factor which has no relation to a machine. I do not mean to disparage in the least the importance of good lighting, but in evaluating the effects of external factors in the performance of visual tasks one must be cautious in using the concept of a "human seeing machine" or of the eye as a "seeing machine."

Book Reviews

Proceedings of the First Clinical ACTH Conference. John R. Mote, Editor. Pp. 607. The Blakiston Company (Division of Doubleday, Doran & Company, Inc.), 1012 Walnut St., Philadelphia 5, 1950.

This 600 page volume, apparently the first of a series, can conveniently be divided into two sections. The first deals chiefly with the physiologic effects of adrenocorticotropic hormone (ACTH), as exhibited by normal persons and as studied in patients treated for various diseases. It mentions the effect of ACTH on the total eosinophil count and the total lymphocyte count; its effect on elevated blood pressure; its effect on protein and carbohydrate metabolism and its effect on electrolytes, namely, retention of sodium and chlorides and fluids with reduced serum potassium levels.

The second part deals with the effects of ACTH on certain specific diseases. These include rheumatoid arthritis, gout, rheumatic fever, lupus erythematosus, myasthenia gravis, nephritis, nephrosis, spontaneous hypoglycemia, allergic states, lymphomas, periarteritis nodosa and ulcerative colitis, which seem to be at least temporarily benefited. Conditions such as tuberculosis, cancer, dermatomyositis, poliomyelitis scleroderma and schizophrenia seem to be very little affected.

This book presents an excellent review of the subject and should serve as an excellent source of material for any one interested in ACTH therapy.

Occupational Eye Diseases and Injuries. By Joseph Minton. Price, $4.50. Pp. 184, with 24 illustrations. Grune & Stratton, Inc., 381 4th Ave., New York 16, 1949.

This small book describes the practical medical aspects of occupational disturbances of the eye. It appears most suited to the needs of the industrial physician but should also be useful to ophthalmologists and to some extent to industrial nurses and social service workers. In a systematic manner there are discussed the characteristics of injuries to the eye from various forms of trauma, from chemicals and from radiant energy. The suitability of various degrees of visual acuity to types of employment is assessed, with special attention to monocular and blind workers. The influences of light and color and the use of ocular protective devices are described. The most significant aspects of these various subjects are succinctly presented, and the general descriptions are frequently illustrated by means of specific cases. Much is contributed to the general authoritativeness of the material by the author's first hand familiarity with the circumstances of industrial risks and his wide acquaintance among British industrial physicians, from whom a great deal of the practical information and case material was obtained.

Considerable attention is given to the medicolegal aspects of ocular disturbances, particularly in relation to workmen's compensation, and, while in principle this is of international interest, specific information has been restricted to the provisions of the laws and regulations of Great Britain.

In discussion of traumatic injuries of the eye, most of the recognized types of injury and their complications are briefly but well described, and the forms of treatment recommended are those generally accepted. Chemical injuries of the eye are described from the clinical standpoint, with little reference to what is known of their mechanism. The treatment advised is generally conservative, the various unproved therapeutic measures which have been urged elsewhere in the literature being largely avoided. Curiously, however, repeated recommendation is made for irrigation with 5 to 10 per cent ammonium chloride solution, without adequate explanation of why this particular solution is preferred. An up-to-date survey of chemical hazards to the cornea and conjunctiva includes a brief description of some newly recognized irritants in the pharmaceutical trade and a recounting of a successful engineering solution to the recurring problem of "sore eyes" from hydrogen sulfide in viscose rayon manufacture. The section on systemic poisons suffers somewhat by comparison, because this chapter appears to have been derived mostly from the older literature. An impression is given that severe ocular disturbances are to be encountered much more commonly in poisoning by trichloroethylene, lead and benzene than is generally held to be the case at present. Methyl alcohol poisoning is described without mention of the important role of acidosis or of the growing recognition of the effectiveness of alkalization therapy.

In connection with radiation hazards, the discussion of glass blower's cataract is particularly noteworthy, although primarily historical. The same applies to the description of miner's nystagmus. The occupational aspects of visual acuity and monocular vision are elucidated largely on the basis of the author's own investigations. Discussion of the influences of lighting and color in industry seems to be based primarily on common sense. Most commendably, there is none of the sensationalism with which this subject has been treated in some quarters.

On the whole, this book constitutes a useful and generally authoritative guide to "occupational eye diseases and injuries," and, in fact, to somewhat more than is indicated in the title.

NOTICE

The index for Volume 43 will be mailed with the July 1950 number.

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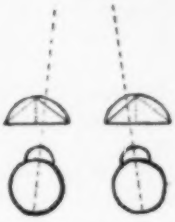

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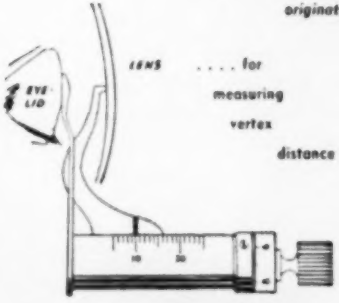

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E	4.00 6.00 8.00	× × ×	× × ×				
K	4.50 6.50 7.50 8.50 9.50	× × × × ×	× × × × ×	× × × ×	×	× ×	× ×
B	Plano 4.50 6.50 8.50	× × × ×	× × × ×	× ×		× ×	×
AL	4.00 6.00	× ×	× ×				
X	4.00 6.00	× ×	× ×	× ×			
T	6.50	×	×				
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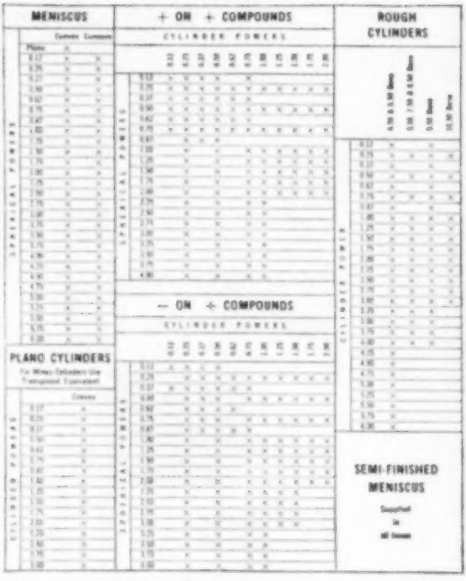

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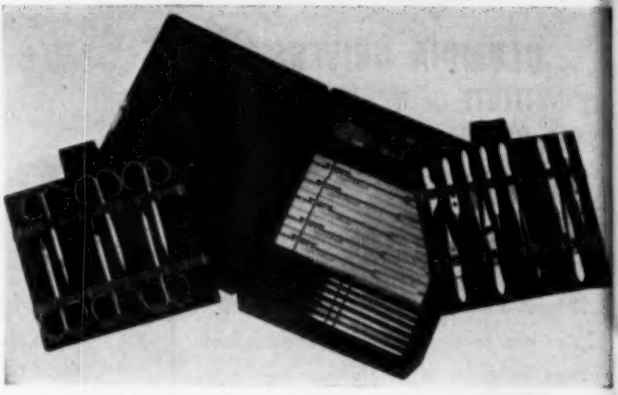

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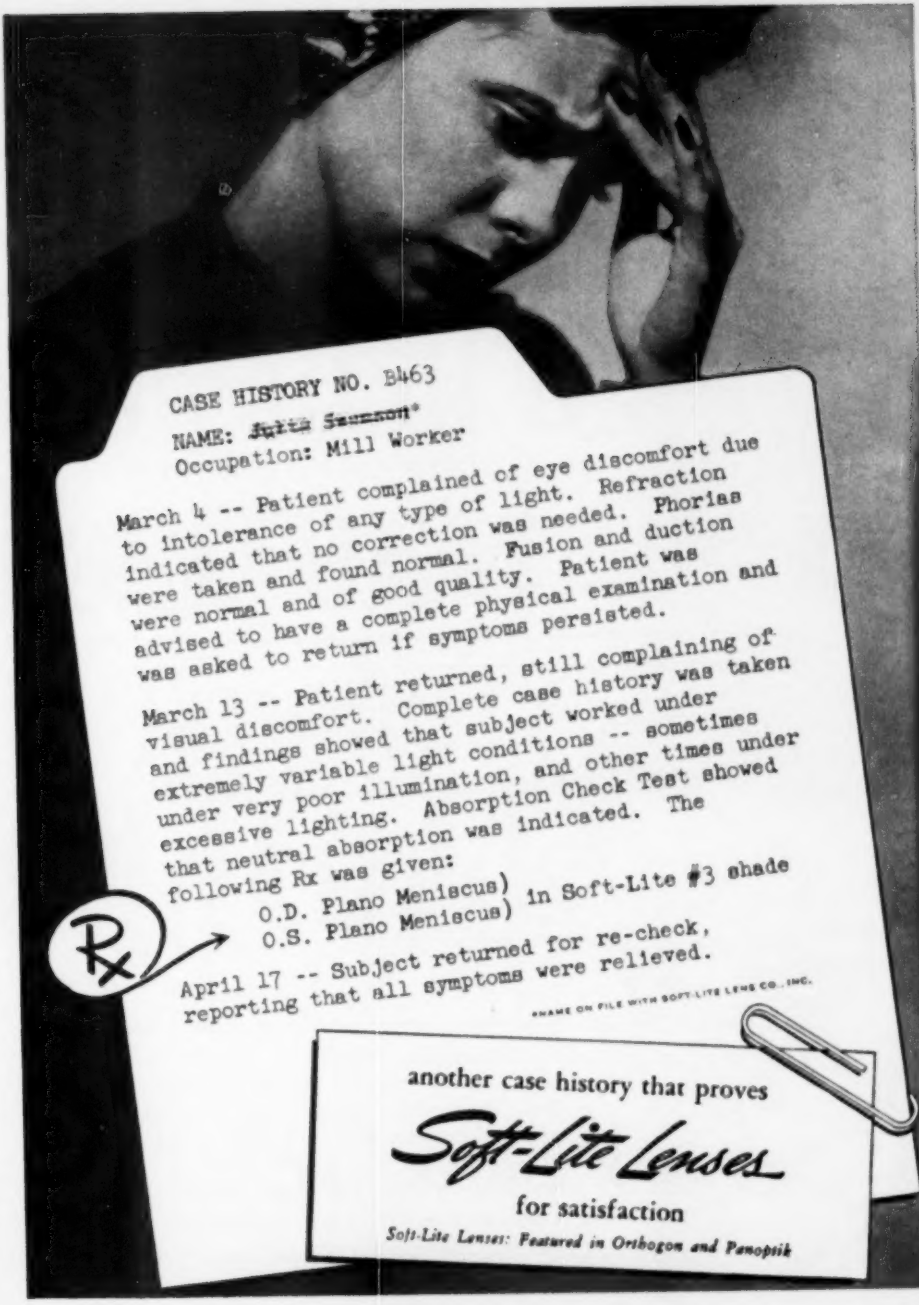
CASE HISTORY NO. B463
NAME: Julia Shannon*
Occupation: Mill Worker
March 4 -- Patient complained of eye discomfort due to intolerance of any type of light. Refraction indicated that no correction was needed. Phorias were taken and found normal. Fusion and duction were normal and of good quality. Patient was advised to have a complete physical examination and was asked to return if symptoms persisted.
March 13 -- Patient returned, still complaining of visual discomfort. Complete case history was taken and findings showed that subject worked under extremely variable light conditions -- sometimes under very poor illumination, and other times under excessive lighting. Absorption Check Test showed that neutral absorption was indicated. The following Rx was given:
O.D. Plano Meniscus)
O.S. Plano Meniscus) in Soft-Lite #3 shade
Rx
April 17 -- Subject returned for re-check, reporting that all symptoms were relieved.
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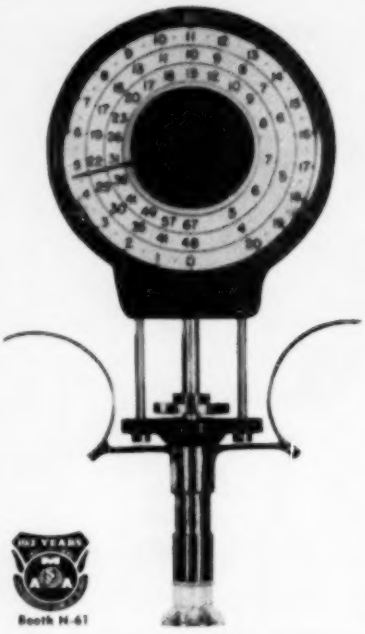

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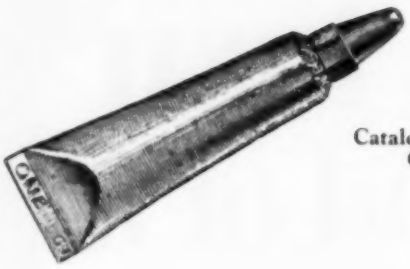

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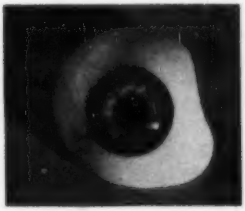

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